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(54) Title: DEAZAPURINE NUCLEOSIDE ANALOGS AND THEIR USE AS THERAPEUTIC AGENTS

(57) Abstract: Methods, compositions, and uses for various deazapurine nucleoside libraries and library compounds are provided. Particularly preferred deazapurine nucleosides include 7-deazapurine nucleosides, 7-deaza-8-azapurine nucleosides, toyocamycin nucleoside analogs, 3-deazapurine nucleosides, and 9-deazapurine nucleosides, while preferred uses especially inlcude use of such compounds as pharmacological, and particularly antiviral agents.

DEAZAPURINE NUCLEOSIDE ANALOGS AND THEIR USE AS THERAPEUTIC AGENTS

This application claims the benefit of U.S. provisional patent application with the serial number 60/350296, filed January 17, 2002, which is incorporated by reference herein.

Field of The Invention

The field of the invention is nucleoside analogs, and is especially directed towards various deazapurine nucleosides and their therapeutic use, particularly for treatment of viral infections with HCV, HRV, RSV, HIV, HBV, as well as viruses in the families of Flaviviridae, Paramyxoviridae, Orthomyxoviridae, Picornaviridae, Bunyaviridae, Arenaviridae, and Herpesviridae.

Background of The Invention

Nucleosides, and especially purine-type nucleosides and their analogs interact with many biological targets, and some nucleoside analogues have been used as antimetabolites for treatment of cancers and viral infections. After entry into the cell, many nucleoside analogues can be phosphorylated to monophosphates by nucleoside kinases, and then further phosphorylated by nucleoside monophosphate kinases and nucleoside diphosphate kinases to give nucleoside triphosphates. Once a nucleoside analogue is converted to its triphosphate inside the cell, it can be incorporated into DNA or RNA. Incorporation of certain unnatural nucleoside analogues into nucleic acid replicates or transcripts can interrupt gene expression by early chain termination or by interfering with the function of the modified nucleic acids. In addition, certain nucleoside analogue triphosphates are very potent, competitive inhibitors of DNA or RNA polymerases, which can significantly reduce the rate at which the natural nucleoside can be incorporated. Many anti-HIV nucleoside analogues fall into this category, including 3'-*C*-azido-3'-deoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyinosine, and 2',3'-didehydro-2',3'-dideoxythymidine.

Various purine-type and other nucleoside analogues can also act in other ways, for example, causing apoptosis of cancer cells and/or modulating immune systems. In addition to nucleoside antimetabolites, a number of nucleoside analogues that show very potent anticancer and antiviral activities act through still other mechanisms. Some well-known nucleoside anticancer drugs are thymidylate synthase inhibitors such as 5-fluorouridine, and

adenosine deaminase inhibitors such as 2-chloroadenosine. A well-studied anticancer compound, neplanocin A, is an inhibitor of S-adenosylhomocysteine hydrolase, which shows potent anticancer and antiviral activities.

Unfortunately, many nucleoside analogues that can inhibit tumor growth or viral infections are also toxic to normal mammalian cells, primarily because these nucleoside analogues lack adequate selectivity between the normal cells and the virus-infected host cells or cancer cells. For this reason, many otherwise promising nucleoside analogues fail to become therapeutics in the treatment of various diseases.

Selective inhibition of cancer cells or host cells infected by viruses has been an important subject for some time, and tremendous efforts have been made to search for more selective nucleoside analogues. In general, however, a large pool of nucleoside analogues is thought to be necessary in order to identify highly selective nucleoside analogues. Unfortunately, the classical method of synthesizing nucleosides and nucleotides having desired physiochemical properties, and then screening them individually, takes a significant amount of time to identify a lead molecule. Although thousands of nucleoside analogues were synthesized over the past decades, if both sugar and base modifications are considered, many additional analogues are still waiting to be synthesized.

During the last few years, combinatorial chemistry has been used to generate huge numbers of organic compounds other than nucleosides, nucleotides, and their analogs resulting in large compound libraries. If nucleosides, nucleotides, and their analogs could be made through a combinatorial chemistry approach, a large number of such compounds could be synthesized within months instead of decades and large libraries could be developed. A combinatorial chemistry approach to nucleosides may also encourage a focus beyond previously addressed biological targets. For example, in the past nucleoside analogues were usually designed as potential inhibitors of DNA or RNA polymerases and several other enzymes and receptors, including inosine monophosphate dehydrogenase, protein kinases, and adenosine receptors. If a vast number of diversified nucleoside analogues could be created, their uses may be far beyond those previously recognized biological targets, which would open a new era for the use of nucleoside analogues as human therapeutics.

The generation of combinatorial libraries of chemical compounds other than nucleosides, nucleotides, and their analogs by employing solid phase synthesis is well known

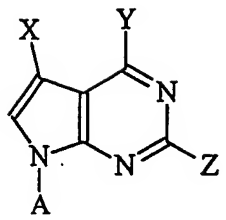
in the art. For example, Geysen, et al. (*Proc. Natl. Acac. Sci. USA*, 3998 (1984)) describes the construction of a multi-amino acid peptide library; Houghton, et al. (*Nature*, 354, 84 (1991)) describes the generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery; Lam, et al. (*Nature*, 354, 82 (1991)) describes a method of synthesis of linear peptides on a solid support such as polystyrene or polyacrylamide resin. Although a combinatorial chemistry approach has been proven to work well with many types of compounds, there are numerous problems with the generation of nucleoside libraries. Among numerous other difficulties, most nucleoside analogues contain a sugar moiety and a nucleoside base, which are linked together through a glycosidic bond. The formation of the glycosidic bond can be achieved through a few types of condensation reactions. However, most of the reactions do not give a very good yield of desired products, which may not be suitable to the generation of nucleoside libraries.

Moreover, the glycosidic bonds in many nucleosides are in labile to acidic condition, and many useful reactions in combinatorial chemistry approaches cannot be used in the generation of nucleoside analogue libraries. As a result, many researchers have focused their attention to areas in pharmaceutical chemistry that appear to present an easier access to potential therapeutic molecules, and there seems to be a lack of methods for generating libraries of nucleosides and nucleotides using solid phase synthesis. Therefore, there is still a need to provide new nucleoside compounds and methods for generation of nucleoside and nucleotide libraries.

Summary of the Invention

The present invention is directed to nucleoside analog libraries, library compounds, and their methods of use. Particularly contemplated nucleoside analog libraries will include library compounds with a modified sugar portion (most preferably modified at the C2'-position) and/or a modified purine base.

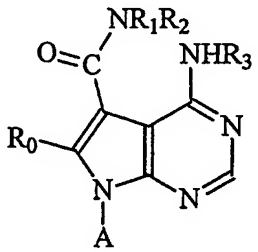
Thus, in one aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 1**



Formula 1

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2'-beta-methylribofuranose; wherein X is H, alkyl (optionally substituted), CN, C(R')NR"R'", NR"R'", NR"NR"R'", NHO-alkyl, N_3, S-alkyl, S-alkenyl, S-alkynyl (all of which may be optionally substituted), O-alkyl, O-alkenyl, O-alkynyl (all of which may be optionally substituted), or ONH_2; wherein Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'" ; wherein Z is H or NH_2; and in which R' is O, NH, NOH, or S, and R" and R'" are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl (all of which may be optionally substituted).

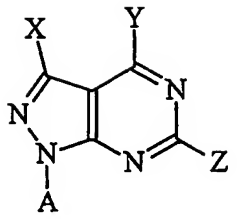
In another aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 2**



Formula 2

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2',3'-beta-dimethylribofuranose; wherein R_0, R_1, R_2, and R_3 are independently H, OH, halogen, alkyl, alkenyl, alkynyl, or aryl (all of which may be optionally substituted).

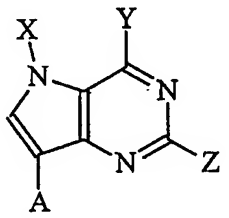
In a further aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 3**



Formula 3

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2'-beta-methylribofuranose; wherein X is H, alkyl (optionally substituted), CN, C(R')NR"R'", C(O)OR", or NR"R'"; wherein Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'" ; wherein Z is H, NH_2, NHC(O)R", NHNHC(O)R", NHNHC(S)R", or $NHS(O)_2R$", and in which R' is O, NH, NOH, or S, and R" and R'" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be optionally substituted).

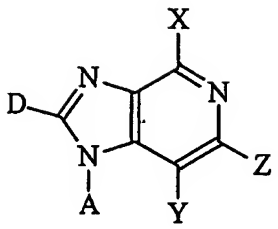
In a still further aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 4**



Formula 4

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2'-beta-methylribofuranose; wherein X is H, alkyl (optionally substituted), CN, C(R')NR"R'", C(O)OR", or NR"R'"; wherein Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'" ; wherein Z is H, NH_2, NHC(O)R", NHNHC(O)R", NHNHC(S)R", or $NHS(O)_2R$", and in which R' is O, NH, NOH, or S, and R" and R'" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be optionally substituted).

In yet another aspect of the inventive subject matter, contemplated compounds may have a structure according to **Formula 5**

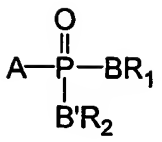


Formula 5

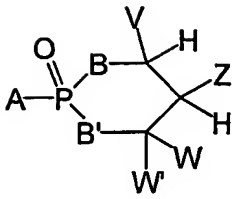
wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2',3'-beta-dimethylribofuranose; wherein D is H, halogen, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted); wherein Y is H, alkyl, alkenyl, alkynyl, aryl (all of which may be optionally substituted); wherein X is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'" ; wherein Z is H or NH_2, and in which R' is O, NH, NOH, or S, and R" and R'" are independently H, OH, or alkyl, alkenyl, alkynyl, aryl (all of which may be optionally substituted).

Further contemplated compounds also include phosphorylated forms (preferably at the 5'-atom), prodrugs, and/or metabolites of the above compounds, and in especially preferred aspects, such compounds may include a moiety (*e.g.*, a cyclic phosphate, a cyclic phosphonate, a cyclic phosphoamidate, or a non-cyclic phosphate (di-) ester) that is covalently coupled to the C2'-atom, C3'-atom, and/or C5'-atom (thereby replacing the corresponding OH group), wherein at least part of the moiety may be preferentially cleaved from the compound in a target cell or target organ.

Therefore, in a further aspect of the inventive subject matter, preferred moieties will have a structure according to **Formulae M1** or **M2**, wherein A, B, B', V, W, W', and Z are defined as in the section entitled "Contemplated Compounds" below. Yet further contemplated prodrugs include SATE (S-acyl-thio-ethyl) and pivalic acid ester-prodrug forms of contemplated compounds.



M1



M2

In a still further aspect of the inventive subject matter, a pharmaceutical composition includes contemplated compounds at a concentration effective to reduce viral propagation of a virus in a patient infected with the virus (*e.g.*, HCV virus, an HRV virus, an RSV virus, an HIV virus, and an HBV virus). Contemplated compositions may further comprise a second pharmacologically active molecule, and particularly preferred molecules include a cytokine (and fragments thereof), immunomodulators, and antibodies.

Consequently, the inventors contemplate a method of treating a viral infection in a patient in which contemplated compounds are administered to the patient in an amount effective to reduce viral propagation. Viewed from another perspective, the inventors contemplate a method of reducing viral propagation in a cell infected with a virus, wherein contemplated compounds present the cell in an amount effective to reduce viral propagation.

Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention.

Detailed Description

The inventors have discovered that various nucleoside analogs, and especially various deazapurine nucleoside analogs, may be employed as therapeutic molecules, and especially as antiviral agents (*e.g.*, against HCV).

The term "nucleoside library" as used herein refers to a plurality of chemically distinct nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs wherein at least some of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs include, or have been synthesized from a common precursor.

For example, a plurality of nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs that were prepared from a protected ribofuranose as a building block/precursor is considered a nucleoside library under the scope of this definition. Therefore, the term "common precursor" may encompass a starting material in a first step in a synthesis as well as a synthesis intermediate (*i.e.*, a compound derived from a starting material). In another example, at least one step in the synthesis of one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs is concurrent with at least one step in the synthesis of another one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and synthesis is preferably at least partially automated. In contrast, a collection of individually synthesized nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and especially a collection of compounds not obtained from a nucleoside library, is not considered a nucleoside library because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs will not have a common precursor, and because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs are not concurrently produced.

It is further generally contemplated that the complexity of contemplated libraries is at least 20 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, more typically at least 100 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, and most typically at least 1,000 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs. Consequently, a typical format of a nucleoside library will include multi-well plates or a plurality of small volume (*i.e.*, less than 1 ml) vessels coupled to each other. The term "library compound" as used herein refers to a nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog within a nucleoside library.

The term "nucleoside" refers to all compounds in which a heterocyclic base is covalently coupled to a sugar, and an especially preferred coupling of the nucleoside to the sugar includes a C1'-(glycosidic) bond of a carbon atom in a sugar to a carbon or heteroatom (typically nitrogen) in the heterocyclic base. The term "nucleoside analog" as used herein refers to all nucleosides in which the sugar is not a ribofuranose and/or in which the heterocyclic base is not a naturally occurring base (*e.g.*, A, G, C, T, I, etc.). It should further be particularly appreciated that the terms nucleoside and nucleoside analog also include all prodrug forms of a nucleoside or nucleoside analog, wherein the prodrug form may be activated/converted to the active drug/nucleoside in one or more than one step, and wherein

the activation/conversion of the prodrug into the active drug/nucleoside may occur intracellularly or extracellularly (in a single step or multiple steps). Especially contemplated prodrug forms include those that confer a particular specificity towards a diseased or infected cell or organ, and exemplary contemplated prodrug forms are described in "Prodrugs" by Kenneth B. Sloan (Marcel Dekker; ISBN: 0824786297), "Design of Prodrugs" by Hans Bundgaard (ASIN: 044480675X), or in copending US application number 09/594410, filed 06/16/2000, all of which are incorporated by reference herein.

Similarly, the term "nucleotide" as used herein refers to a nucleoside that is coupled to a 5'-phosphate group (or modified phosphate group, including phosphonate, thiophosphate, phosphate ester, etc.). Consequently, the term "nucleotide analog" refers to a nucleoside analog that is coupled to a 5'-phosphate group (or modified phosphate group, including phosphonate, thiophosphate, phosphate ester, etc.).

As used herein, the terms "heterocycle" and "heterocyclic base" are used interchangeably herein and refer to any compound in which a plurality of atoms form a ring via a plurality of covalent bonds, and wherein the ring includes at least one atom other than a carbon atom. Particularly contemplated heterocyclic bases include 5- and 6-membered rings with nitrogen, sulfur, or oxygen as the non-carbon atom (*e.g.*, imidazole, pyrrole, triazole, dihydropyrimidine). Further contemplated heterocylces may be fused (*i.e.*, covalently bound) to another ring or heterocycle, and are thus termed "fused heterocycle" as used herein. Especially contemplated fused heterocycles include a 5-membered ring fused to a 6-membered ring (*e.g.*, purine, 7-deazapurine, 7-deaza-8-azapurine, 3-deazapurine, or 9-deazapurine).

Still further contemplated heterocyclic bases may be aromatic, or may include one or more double or triple bonds. Moreover, contemplated heterocyclic bases may further include one or more substituents other than hydrogen, and especially contemplated substituents include those referenced below. Contemplated heterocycles or substituted heterocycles are typically attached directly to nucleoside bases or sugars, but coupling of the heterocyclic base to the sugar may also include a linker moiety with at least 1-4 atoms between the heterocyclic base and the sugar.

As further used herein, the term "sugar" refers to all carbohydrates and derivatives thereof, wherein particularly contemplated derivatives include deletion, substitution or

addition of a chemical group in the sugar. For example, especially contemplated deletions include 2'-deoxy and/or 3'-deoxy sugars. Especially contemplated substitutions include replacement of the ring-oxygen with sulfur, methylene, or nitrogen, or replacement of a hydroxyl group with a halogen, an amino-, sulfhydryl-, or methyl group, and especially contemplated additions include methylene phosphonate groups, 2'-beta-methyl and/or 3'-beta-methyl groups. Further contemplated sugars also include sugar analogs (*i.e.*, not naturally occurring sugars), and particularly carbocyclic ring systems. The term " carbocyclic ring system" as used herein refers to any molecule in which a plurality of carbon atoms form a ring, and in especially contemplated carbocyclic ring systems the ring is formed from 3, 4, 5, or 6 carbon atoms. Examples of these and further preferred sugars are provided below.

The terms "alkyl" and "unsubstituted alkyl" are used interchangeably herein and refer to any linear, branched, or cyclic hydrocarbon in which all carbon-carbon bonds are single bonds. The term "substituted alkyl" as used herein refers to any alkyl that further comprises a functional group, and particularly contemplated functional groups include nucleophilic (*e.g.*, -NH_2, -OH, -SH, -NC, etc.) and electrophilic groups (*e.g.*, C(O)OR, C(X)OH, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (e.g., -NH_3^+), and halogens (*e.g.*, -F, -Cl), and all chemically reasonable combinations thereof. The terms "alkenyl" and "unsubstituted alkenyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl with at least one carbon-carbon double bond. The term "substituted alkenyl" as used herein refers to any alkenyl that further comprises a functional group, and particularly contemplated functional groups include those discussed above.

Furthermore, the terms "alkynyl" and "unsubstituted alkynyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl or alkenyl with at least one carbon-carbon triple bond. The term "substituted alkynyl" as used herein refers to any alkynyl that further comprises a functional group, and particularly contemplated functional groups include those discussed above. The terms "aryl" and "unsubstituted aryl" are used interchangeably herein and refer to any aromatic cyclic, alkenyl, or alkynyl. The term "substituted aryl" as used herein refers to any aryl that further comprises a functional group, and particularly contemplated functional groups include those discussed above. The term "alkaryl" is employed where the aryl is further covalently bound to an alkyl, alkenyl, or alkynyl.

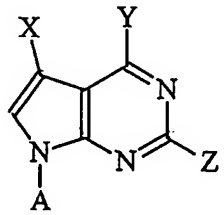
Thus, the term "substituted" as used herein also refers to a replacement of a chemical group or substituent (typically H or OH) with a functional group, and particularly contemplated functional groups include nucleophilic (*e.g.*, $-NH_2$, -OH, -SH, -NC, etc.) and electrophilic groups (*e.g.*, C(O)OR, C(X)OH, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (*e.g.*, $-NH_3^+$), and halogens (*e.g.*, -F, -Cl), and all chemically reasonable combinations thereof.

Contemplated Nucleosides

The present invention is generally directed to various heterocyclic nucleoside libraries and library compounds within these libraries, wherein contemplated compounds may be synthesized by medicinal and combinatorial approaches using solution and/or solid phase strategies. Furthermore, while most of the schemes below depict nucleosides and nucleoside analogs, it should be recognized that all of the contemplated nucleosides and nucleoside analogs may also be phosphorylated (preferably at the C5'-position) to the corresponding nucleotide or nucleotide analogs. Moreover, it should be appreciated that all prodrug forms and metabolites of the compounds according to the inventive subject matter presented herein are also contemplated.

6,7-Disubstituted-7-Deazapurine Nucleoside Libraries and Compounds

In one aspect of the inventive subject matter, contemplated compounds, libraries, and library compounds will generally have a structure according to **Formula 1**



Formula 1

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2'-beta-methylribofuranose; wherein X is H, alkyl (optionally substituted), CN, C(R')NR"R'", NR"R'", NR"NR"R'", NHO-alkyl, N_3, S-alkyl, S-alkenyl, S-alkynyl (all of which may be optionally substituted), or O-alkyl, O-alkenyl, O-alkynyl (all of which may be optionally substituted), or ONH_2; wherein Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-

alkyl, or NR"R'" ; wherein Z is H or NH_2; and in which R' is O, NH, NOH, or S, and R" and R'" are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl (all of which may be optionally substituted).

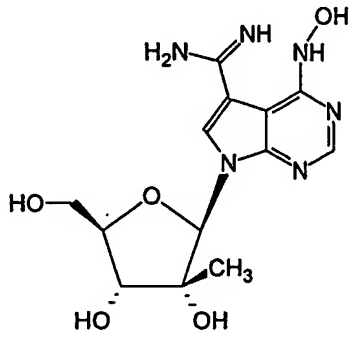
In particularly preferred aspects of the inventive subject matter, the sugar is a ribofuranose in D- or L-configuration, which may in some aspects be further substituted in one or more positions. For example, where the nucleoside analog is employed as a substrate or cosubstrate for an enzyme using nucleotides, contemplated 6,7-disubstituted-7-deazapurine nucleosides may include a phosphate group (or phosphate analog, including phosphonate, phosphoamidate, or thiophosphate) coupled to the C5'-position. Depending on the particular location of the enzyme, the charge of the phosphate group may be masked by chemical modification to facilitate penetration of contemplated compounds across a cell membrane, and suitable modifications include esterification (*e.g.*, pivaloyl ester, or S-acyl-esters), amidation, ether formation, etc. In especially preferred modifications, at least part of the modification is cleaved from the compound once the compound enters a cell (*infra*).

In another example, it is contemplated that sugar modifications may be employed to provide improved biochemical properties to contemplated compounds. For example, where the compound is employed as an inhibitor of an RNA-dependent RNA polymerase (*e.g.*, NS5B of HCV), a 2'-beta modification (and especially a 2'-beta methyl or 2'-beta hydroxymethyl modification may be included to improve antiviral activity. While not wishing to be bound to a particular theory, it is contemplated that such modification improved the selectivity of contemplated compounds to the HCV polymerase (over other polymerases) as well as decreases the Km of the compound (as compared to the same compound without the modification).

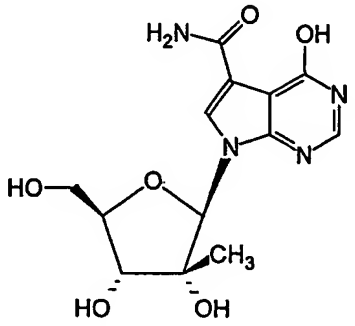
In still further contemplated modifications at the sugar, it should be recognized that all modifications may be employed to increase one or more pharmacological (*e.g.*, half-life time, absorption, bioconversion, etc.) or biochemical parameters (*e.g.*, solubility, electrical charge, selectivity to a structure interacting with contemplated compounds, etc.) of contemplated compounds, and all known modifications are contemplated suitable for use herein. Similarly, it should be recognized that the heterocyclic base may also be modified to increase one or more pharmacological or biochemical parameters of contemplated compounds. For example

suitable modifications on OH groups may include esterifications, or modifications on NH2 groups may include amidations.

Therefore, and among various alternative preferred compounds, particularly preferred compounds may have a structure as shown below.

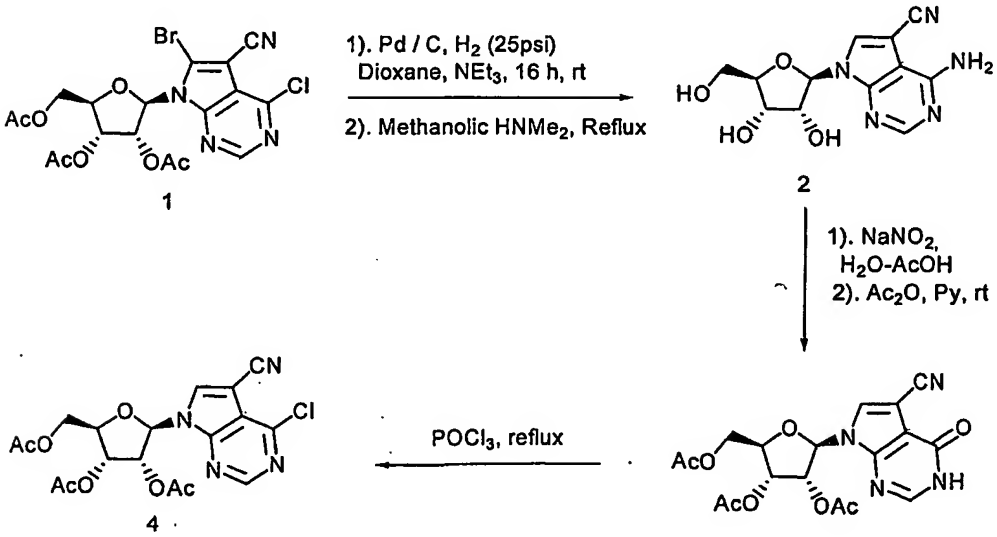


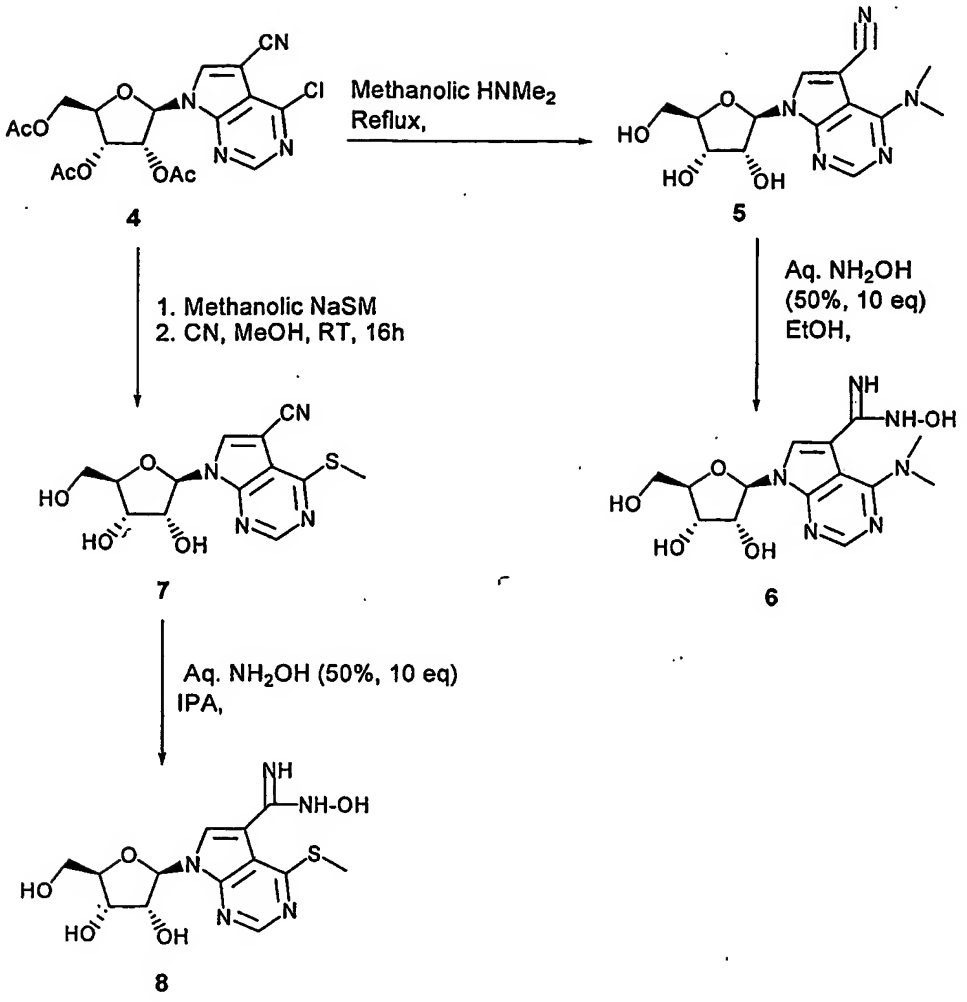
or



With respect to the synthesis of contemplated 6,7-disubstituted-7-deazapurine nucleosides, the inventors discovered that 6,7-disubstituted-7-deazapurine nucleoside libraries and compounds may be prepared following numerous procedures, and various exemplary synthetic routes are depicted below.

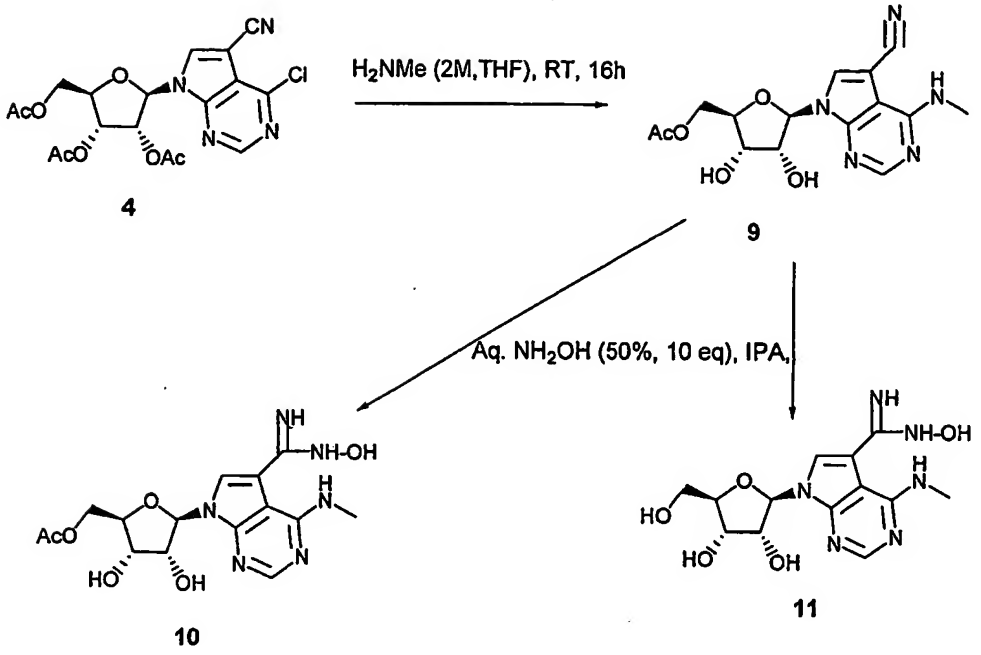
For example, as depicted in **Scheme 1**, 6,7-disubstituted-7-deazapurine nucleosides are prepared from the corresponding C2'-beta-methyl ribonucleoside by replacing a leaving group in 6-position (*e.g.*, Cl) with a suitable nucleophilic agent (*e.g.*, primary or secondary amine, thiol reagent), and by further reacting the CN group in 7-position to the desired substituent (here: hydroxycarbamidine).





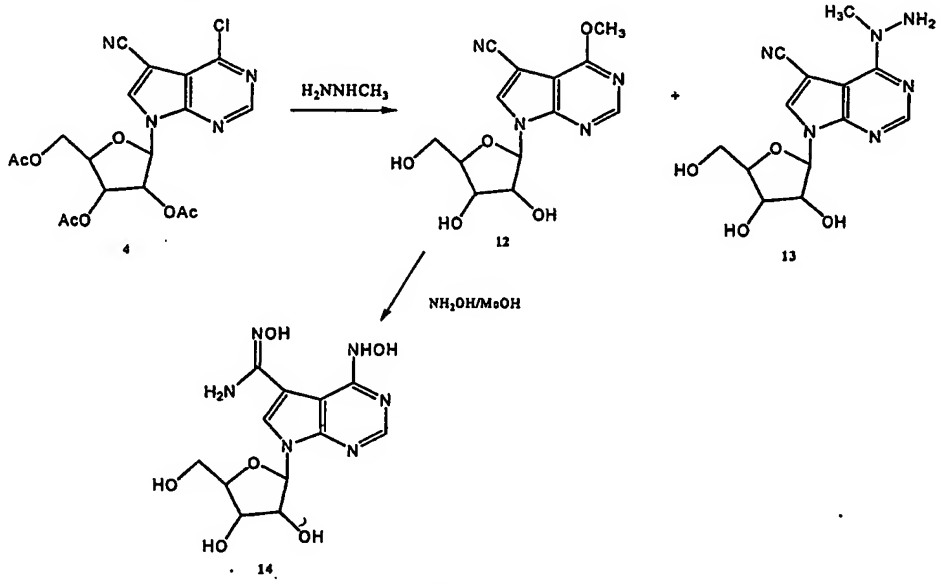
Scheme 1

Of course, it should be recognized that various nucleophilic reagents other than those shown in Scheme 1 above are also suitable, and it is generally contemplated that all reagents are suitable that will replace the leaving group in the 6-position. Among other reagents, suitable alternative nucleophilic reagents are listed below in the section entitled "Experiments and Data". For example, where the nucleophilic reagent comprises a primary amine, 6,7-disubstituted-7-deazapurine nucleosides may be prepared as depicted in **Scheme 2** below.



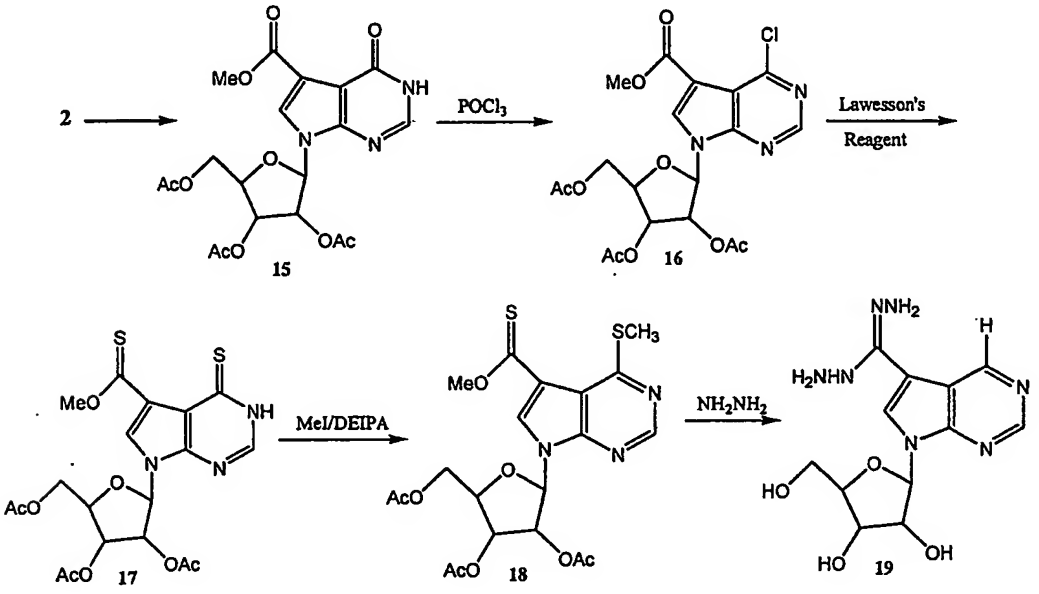
Scheme 2

Alternatively, compound 4 of Scheme 1 may also be derivatized with a secondary amine under conditions that yield the 6-methoxy product and the 6-methylhydrazino product as shown in **Scheme 3** below. Again, a person of ordinary skill in the art will readily recognize that by employing various secondary amines, the chemical nature of the resulting 6-substituents will vary accordingly.



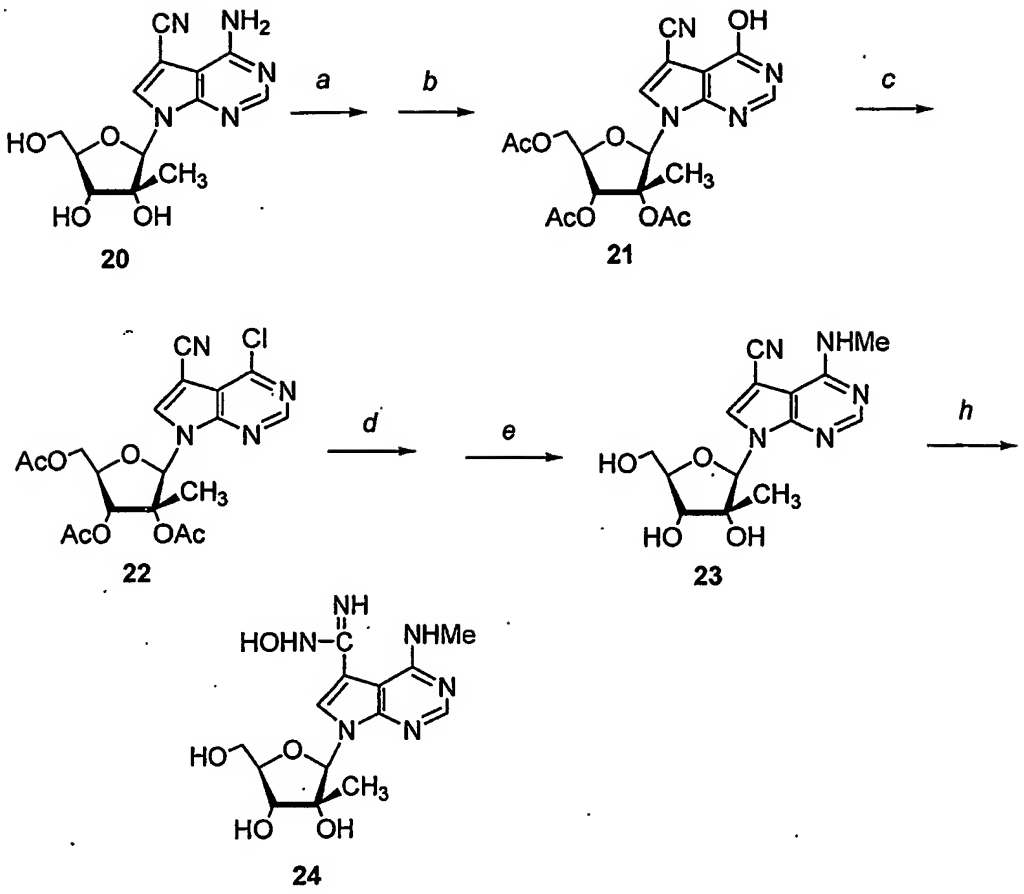
Scheme 3

Similarly, as depicted in **Scheme 4** below, compound 2 of Scheme 1 may be hydrolyzed in methanolic ammonia to the corresponding 6-oxo-7-carboxylate, in which the carbonyl oxygen atoms are then replaced with sulfur atoms. The 6-sulfo group may then be reacted to the corresponding thioether using a variety of reagents (*e.g.*, various alkyl halogenides), while the thiocarbonyl group is further reacted with a hydrazine or hydrazine derivative. Therefore, by varying the 6-sulfo-reactive reagent and the thiocarbonyl-reactive reagent, it should be recognized that numerous 6,7-disubstituted-7-deazanucleosides may be prepared.



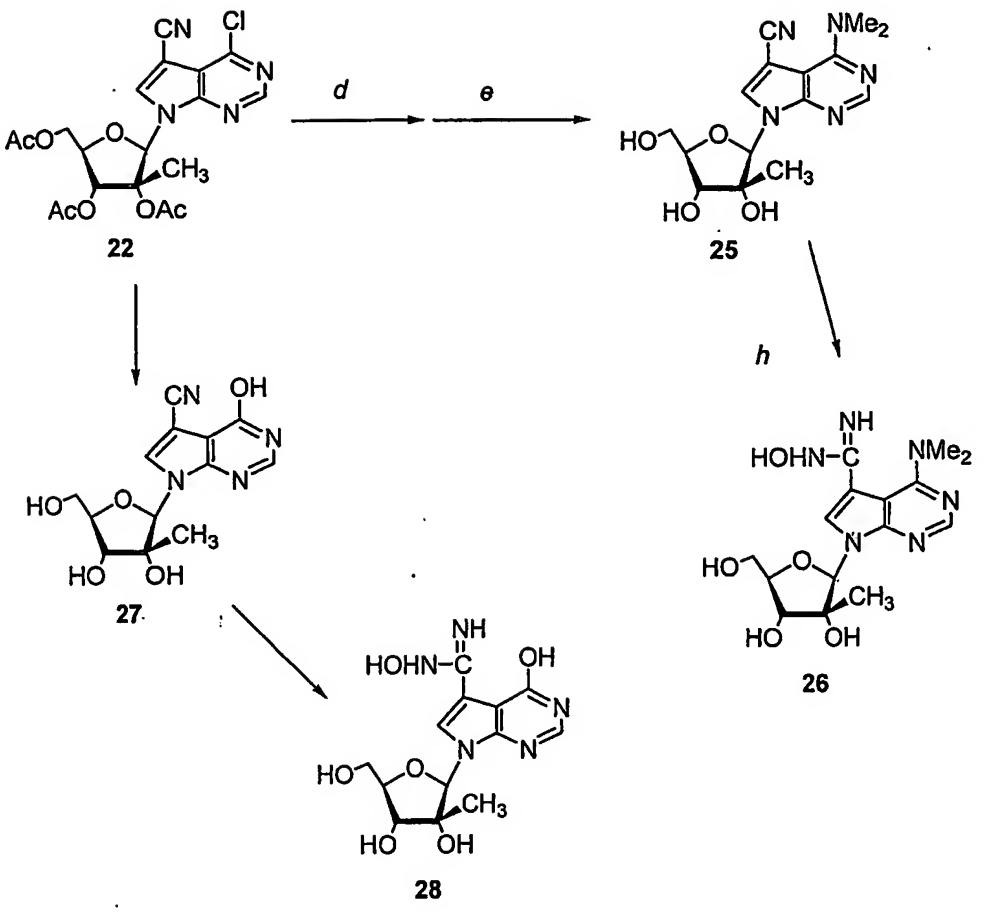
Scheme 4

Where it is especially preferred that the 6,7-disubstituted-7-deazanucleoside is further modified in the sugar portion (*e.g.*, 2'-beta-methyl substituted ribofuranose), a synthetic route as depicted in **Scheme 5** below may be employed in which a suitably substituted nucleoside (*e.g.*, 4-Amino-5-cyano-7-(2′-*C*-methyl-2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine, for synthesis see *Heterocycles* 1992, *33 (1)*, 391-404) is converted to the corresponding 6-Chloro-7-cyano-nucleoside, which is then derivatized in several steps to the desired products. For example, the chloro group may be employed as a leaving group in a nucleophilic aromatic substitution reaction with a desired nucleophilic reagent (*e.g.*, primary or secondary amine, alcohol, or thiol), while the 7-cyano group may be hydrolyzed under mild conditions to the corresponding carboxamide oxime.

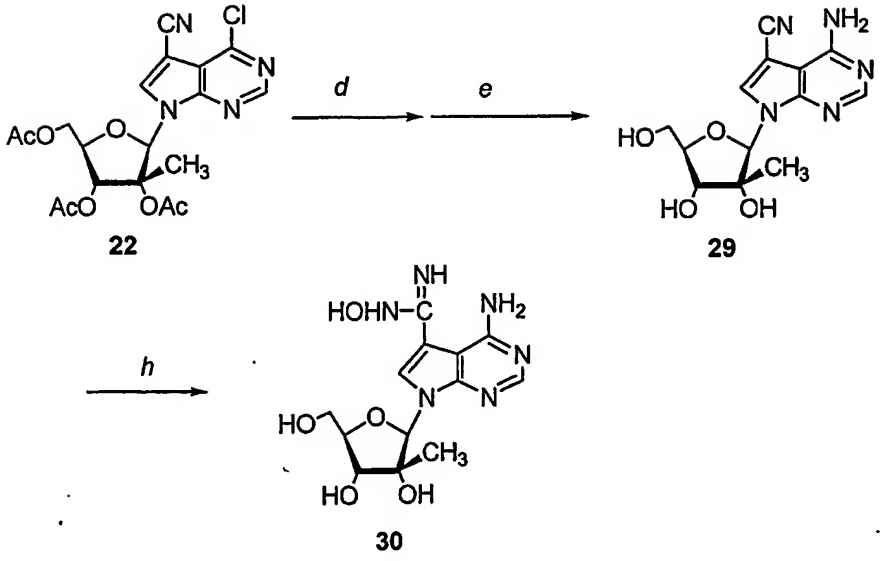


Scheme 5

Alternatively, a secondary amine may be utilized as the nucleophilic reagent, and/or the 6-chloro group may be replaced by OH to generate the corresponding alternative products as exemplified in **Scheme 6** below. Similarly, the 6-chloro group may be replaced by NH_2 to form the corresponding 6-amino product which may be further modified as described above and shown in **Scheme 7** below.

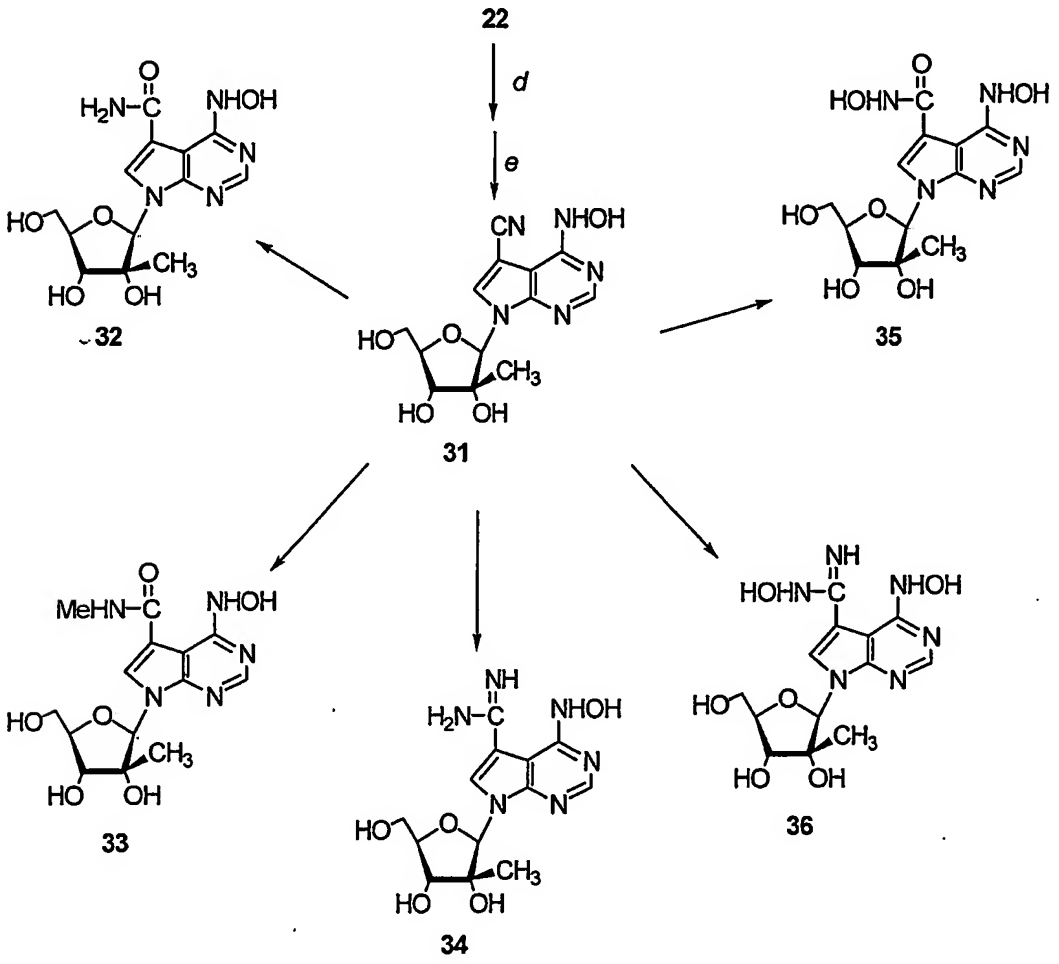


Scheme 6



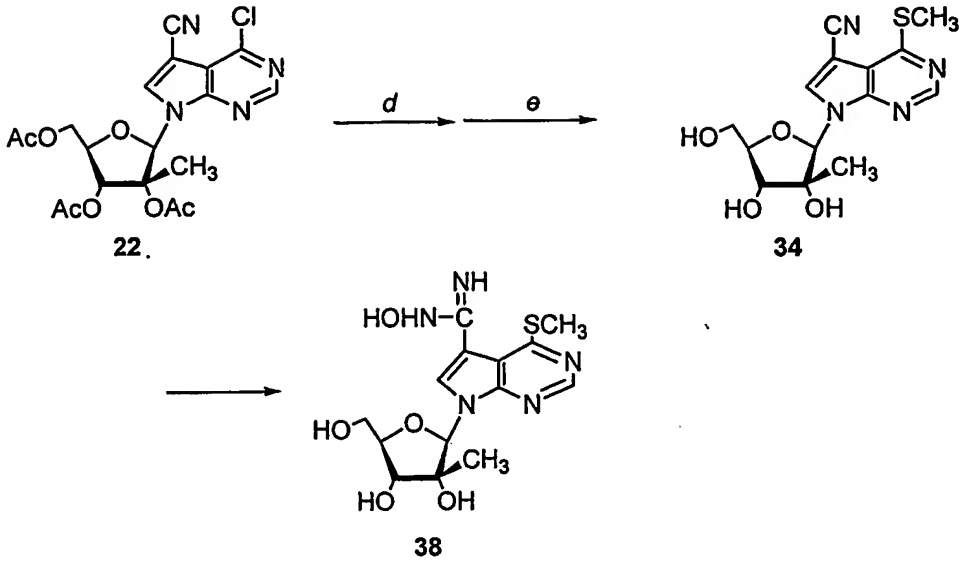
Scheme 7

In still further contemplated alternative synthetic routes of preparing 2'-modified-6,7-disubstituted-7-deazanucleosides, compound 22 of Scheme 7 may be reacted to form the corresponding 7-cyano-6-hydroxylamine compound, which may then serve as a scaffold for further modifications. For example, in particularly preferred aspects, the cyano group is converted to the corresponding carboxamide, substituted carboxamide, carboxamidine, or substituted carboxamidine as depicted in **Scheme 8** below.

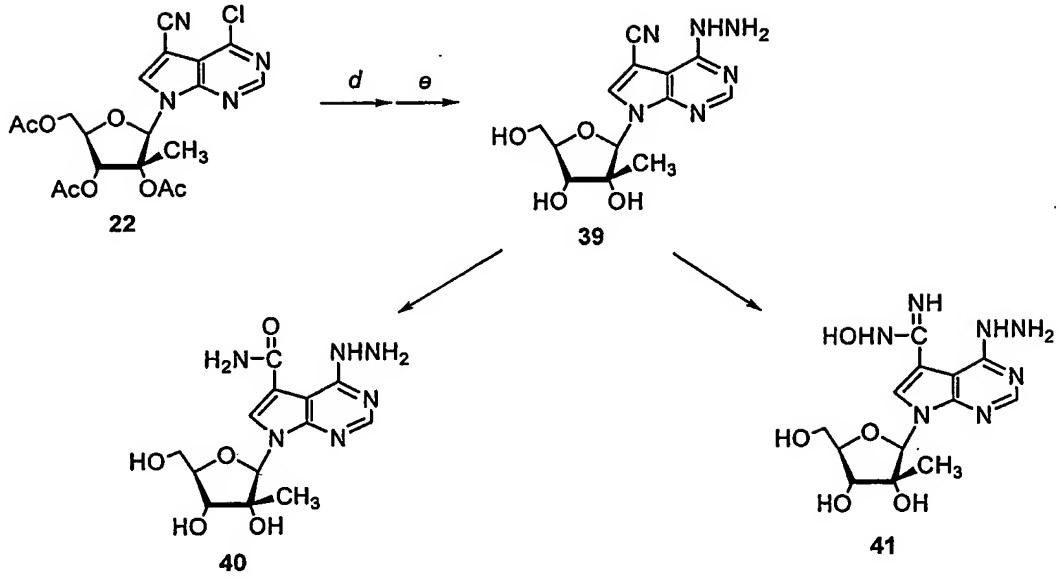


Scheme 8

Nucleophilic reaction of compound 22 with a thiol or (substituted) hydrazine, and subsequent (optional) modification of the cyano group will afford modified nucleosides as depicted in **Schemes 9-10** below, generally following reaction protocols as described above. Again, and as it also applies for the reactions shown above, modification of the reagents will result in the corresponding modified 2'-modified-6,7-disubstituted-7deazapurine.

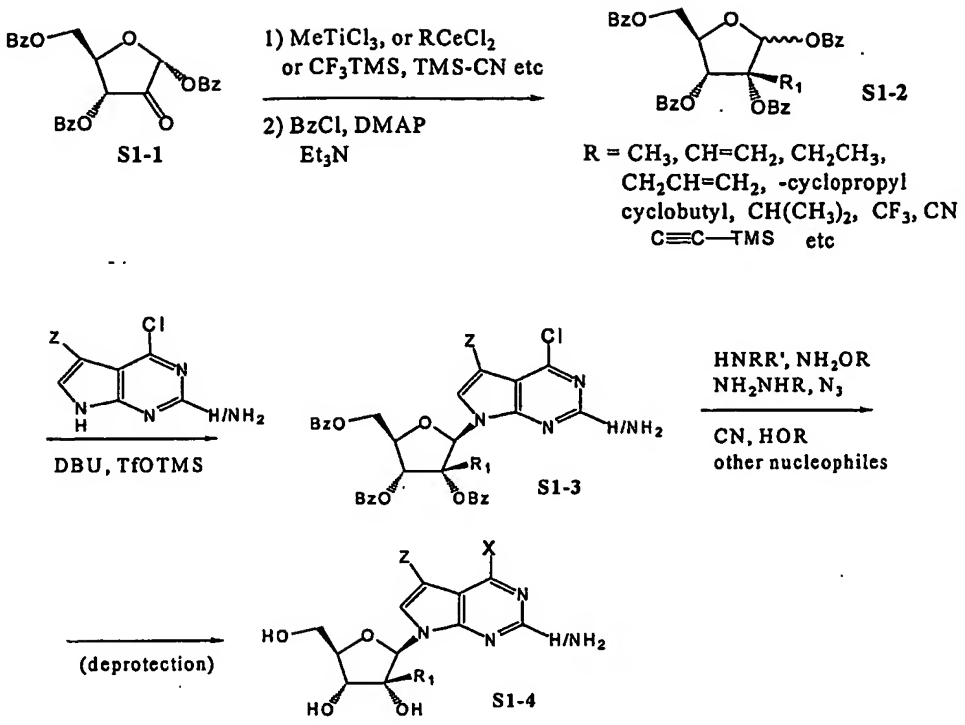


Scheme 9



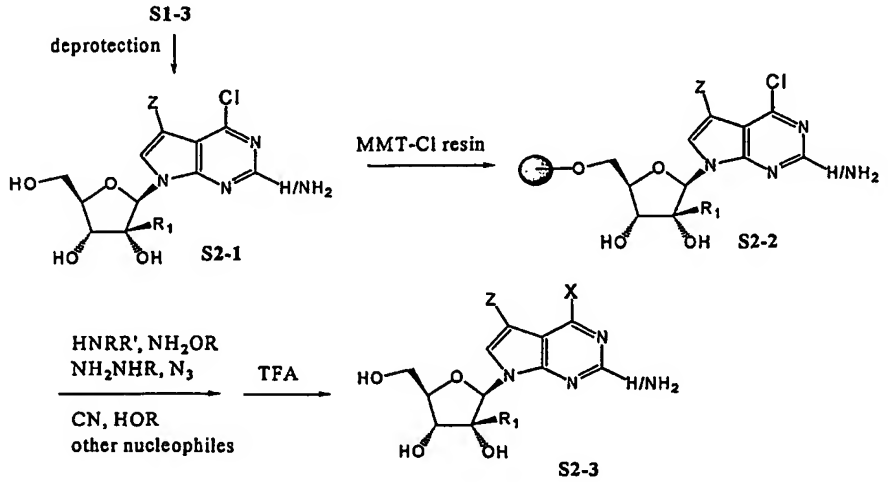
Scheme 10

In still further preferred aspects of the inventive subject matter, 6,7-disubstituted-7-deazapurine nucleoside libraries and compounds may be synthesized as depicted in exemplary **Scheme 11** in which a suitable protected sugar is converted to the respective C2'-modified sugar that is then coupled to a heterocyclic base. The so prepared nucleosides may then be further modified to the corresponding desired compounds.



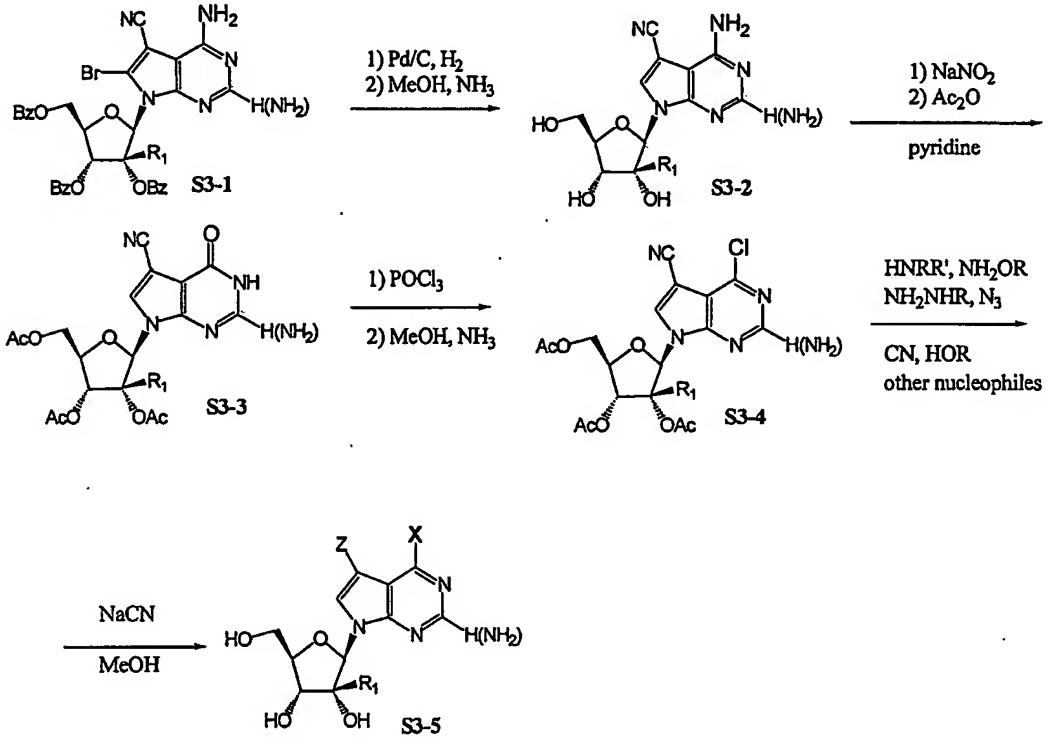
Scheme 11

Alternatively, and especially where it is desirable to perform the synthesis on a solid phase, a similar approach as described in Scheme 11 may be employed. Here, 6,7-disubstituted-7-deazapurine nucleoside libraries and compounds may be synthesized as depicted in exemplary **Scheme 12** in which a suitably protected 7-deazapurine nucleoside is first coupled to a resin and then derivatized following a substantially identical protocol as described for Scheme 11.



Scheme 12

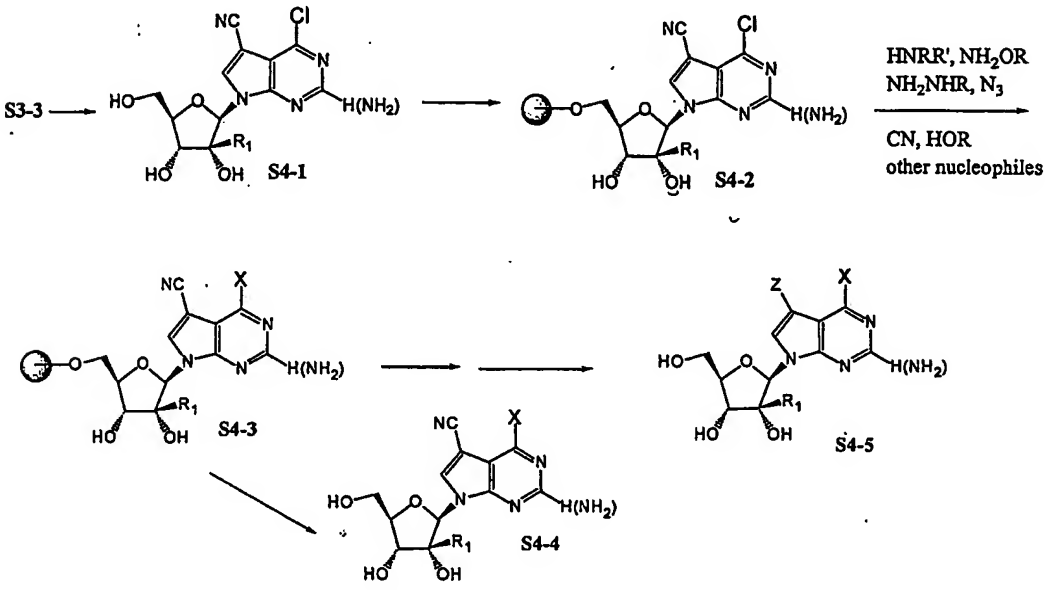
In yet another strategy, and especially where the synthesis starts from a substituted 6-aminopurine heterocyclic base, a synthetic approach as depicted in **Scheme 13** may be utilized in which the 6-amino group is selectively transformed into a keto-carbonyl, which is then replaced by a chlorine. The so prepared product may then be derivatized to the corresponding library compounds.



Scheme 13

Especially preferred reactions involve those in which the 6-position is reacted with an oxygen containing nucleophile (*e.g.*, substituted or unsubstituted alcohol, water) to yield the corresponding substituted or unsubstituted 6-oxygen. Furthermore, it is generally preferred that the substituent in the 7-position comprises a carbonyl atom, and most preferably a carboxamide, a hydroxycarboxamidine, or a carboxamidine.

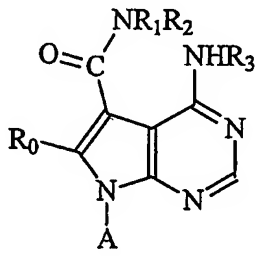
Alternatively, an exemplary synthetic strategy as depicted in **Scheme 14** below may be employed to prepare various substituted 7-deazapurine library compounds on solid support using the substantially similar reaction conditions and protocols as described above.



Scheme 14

Modified Toyocamycin Nucleoside Libraries and Compounds

In another aspect of the inventive subject matter, contemplated compounds, libraries, and library compounds will generally have a structure according to **Formula 2**



Formula 2

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2',3'-beta-dimethylribofuranose; wherein R_0, R_1, R_2, and R_3 are independently H, OH, halogen, alkyl, alkenyl, alkynyl, or aryl (all of which may be optionally substituted).

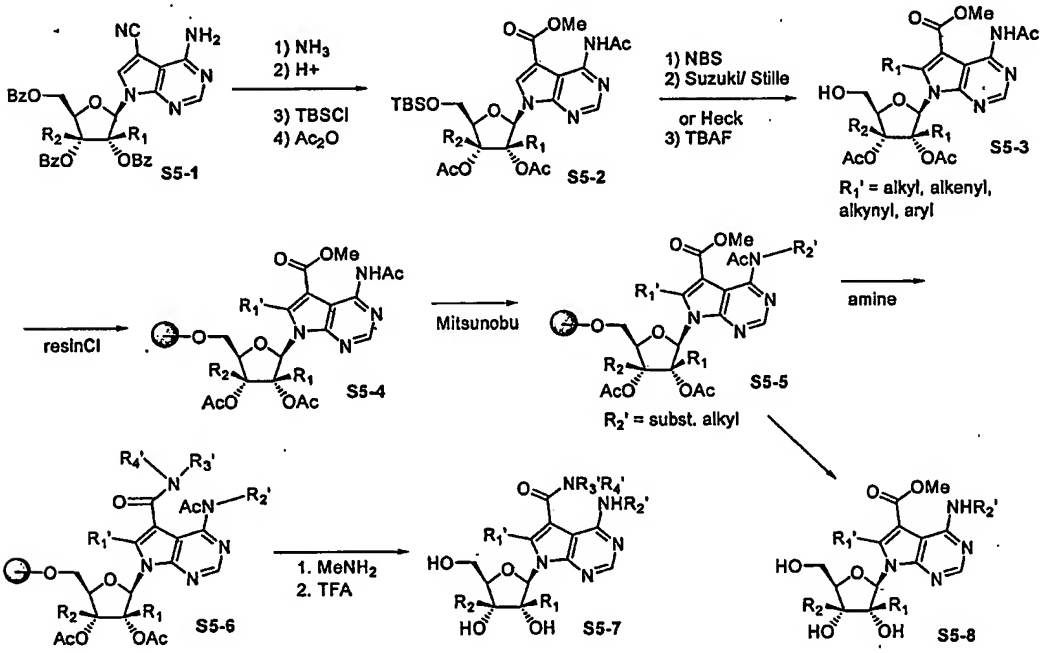
In particularly preferred aspects of the inventive subject matter, the sugar is a ribofuranose in D- or L-configuration, which may in some aspects be further substituted in one or more positions. For example, where the nucleoside analog is employed as a substrate or cosubstrate for an enzyme using nucleotide, contemplated modified toyocamycin nucleosides may include a phosphate group (or phosphate analog, including phosphonate, phosphoamidate, or thiophosphate) coupled to the C5'-position. Depending on the particular location of the enzyme, the charge of the phosphate group may be masked by chemical modification to facilitate penetration of contemplated compounds across a cell membrane, and suitable modifications include esterification (*e.g.*, pivaloyl ester, or S-acyl-esters), amidation, ether formation, etc. In especially preferred modifications, at least part of the modification is cleaved from the compound once the compound enters a cell (*infra*).

In another example, it is contemplated that sugar modifications may be employed to provide improved biochemical properties to contemplated compounds. For example, where the compound is employed as an inhibitor of an RNA-dependent RNA polymerase (*e.g.*, NS5B of HCV), a 2',3-beta (and especially a 2',3'-beta dimethyl) modification may be included to improve antiviral activity. While not wishing to be bound to a particular theory, it is contemplated that such modification improvesthe selectivity of contemplated compounds to the HCV polymerase (over other polymerases) as well as decreases the Km of the compound (as compared to the same compound without the modification).

In still further contemplated modifications at the sugar, it should be recognized that all modifications may be employed to increase one or more pharmacological (*e.g.*, half-life time, absorption, bioconversion, etc.) or biochemical parameters (*e.g.*, solubility, electrical charge, selectivity to a structure interacting with contemplated compounds, etc.) of contemplated compounds, and all known modifications are contemplated suitable for use herein. Similarly, it should be recognized that the heterocyclic base may also be modified to increase one or more pharmacological or biochemical parameters of contemplated compounds. For example suitable modifications on OH groups may include esterifications, or modifications on NH2 groups may include amidations.

With respect to the synthesis of such modified Toyocamycin nucleosides and libraries, the inventors discovered that various synthetic routes may be employed, and exemplary synthetic routes are depicted below in Schemes 15-17. For example, as depicted in

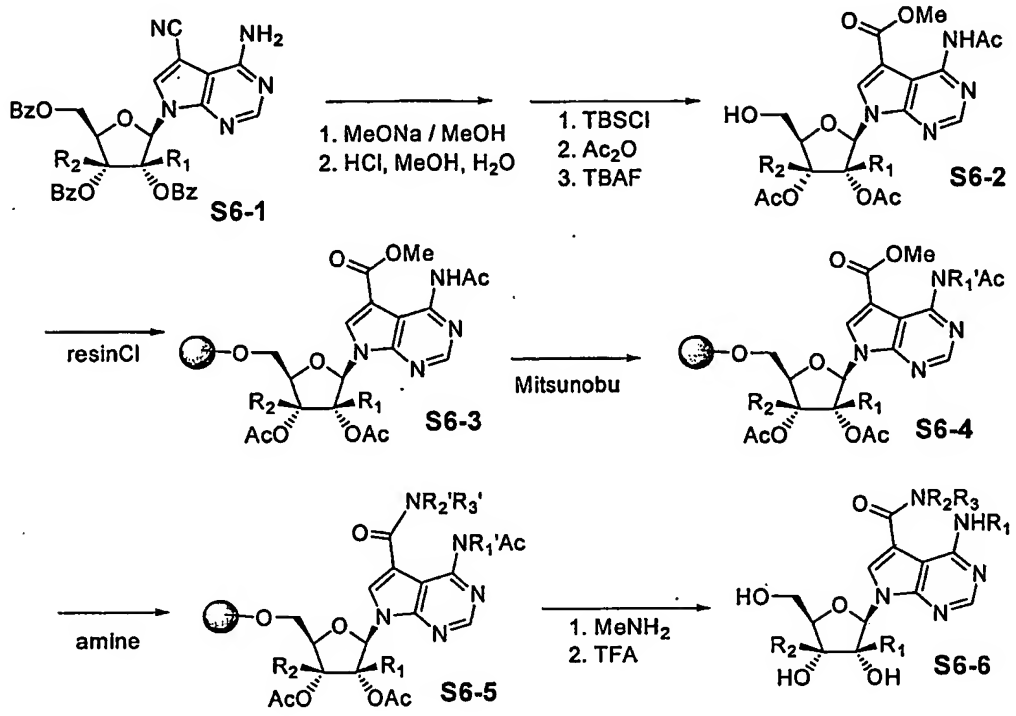
Scheme 15 below, a C_2',C_3'-disubstituted nucleoside precursor (here: protected commercially available Toyocamycin) is modified in various steps to introduce a substituent in the position via Suzuki, Stille, or Heck reaction to produce a first set of derivatized toyocamycin derivatives, and to further derivatize the 6-amino group (where appropriate) via Mitsunobu reaction to produce a second set of derivatized toyocamycin derivatives. Alternatively, or additionally, the carbonyl group in the 7-position may further be modified with various nucleophiles (*e.g.*, primary or secondary amines, thiols, alcohols, Grignard reagents, etc.) to produce a third set of derivatized toyocamycin derivatives. Of course, it should be recognized that depending on the particular choice of reagents (for exemplary reagents in Heck, Stille, Suzuki, and Mitsunobu reagents, see below in the section entitled "Experiments and Data"), numerous products may be achieved. Furthermore, where at least some of the reactions are performed on a solid phase, it should further be recognized that the reactions of Scheme 15 may be employed to create a highly diverse modified toyocamycin library.



Scheme 15

Alternatively, as shown in **Scheme 16** below, modification of the 8-position may be omitted in selected C_2',C_3'-disubstituted toyocamycin libraries, and compounds may be synthesized in a procedure similar to Scheme 15 in which a C_2',C_3'-disubstituted nucleoside

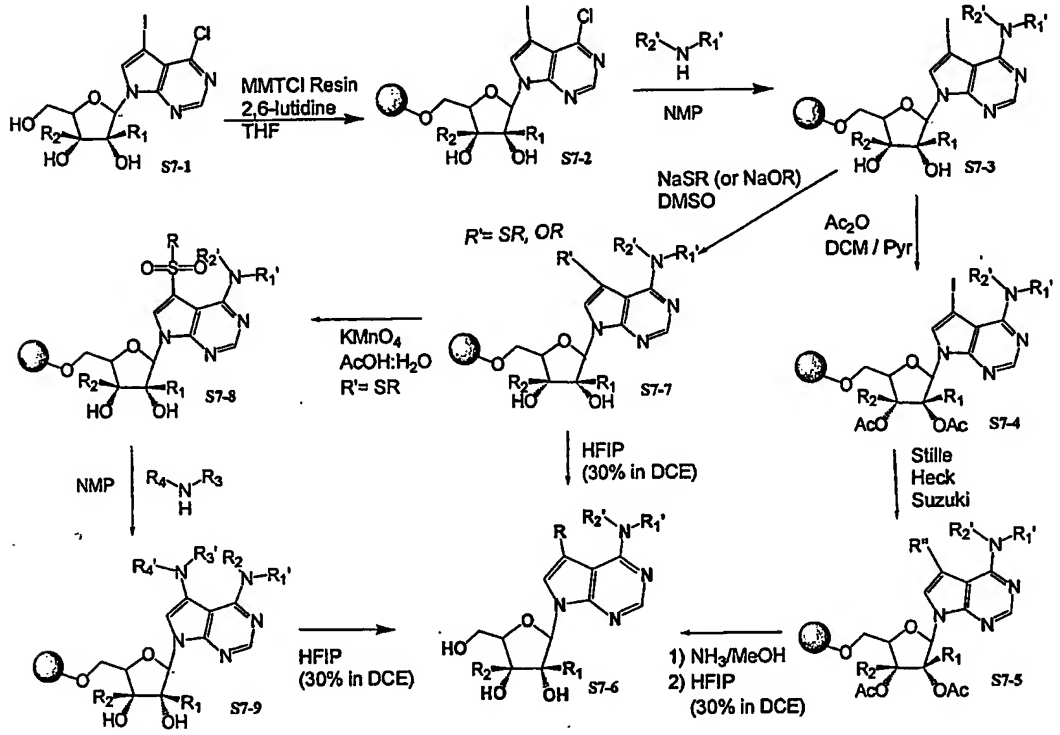
precursor is modified in various steps to introduce and derivatize the 7-carbonyl group and to derivatize the 6-amino group (where appropriate).



Scheme 16

In a still further contemplated aspect of the inventive subject matter, C_2',C_3'-disubstituted modified toyocamycin libraries and compounds may be synthesized as depicted in **Scheme 17** below in which a C_2',C_3'-disubstituted nucleoside precursor with an iodine (or other suitable leaving group) in the 7-position is in one or more reactions replaced by a desired nucleophile, which may then be further modified. Similarly, a leaving group in the 6-position is employed to introduce various substituents to this position. As a person of ordinary skill in the art will readily recognize, the nature of the particular nucleophiles for the introduction of the 6-position substituent may vary significantly, and all known nucleophiles are considered suitable for use herein. However, particularly preferred nucleophiles include primary and secondary amines, thiols, alcohols, and Grignard reagents. Similarly, it should be recognized that the chemical nature of the reagent for the second modification may vary considerably. For example, where the iodine group is replaced in a Heck, Stille, or Suzuki reaction, suitable second reagents may include those exemplified in the section entitled "Experiments and Data" below. On the other hand, where the iodine is replaced with an

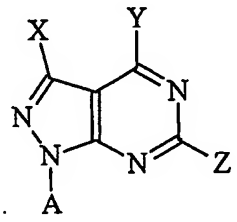
alcohol or thiol, generally contemplated reagents will have the formula RSH or ROH, wherein R is alkyl, alkenyl, alkynyl, alkaryl, or aryl (all of which may further be substituted by one or more substituents). In still further alternative aspects, and especially where the second reagent comprises a thiol, it should be recognized that the thiol substituent in the 7-poition may be oxidized to form a leaving group that is then replaced with a suitable nucleophile.



Scheme 17

7-Deaza-8-Azapurine Nucleoside Libraries and Compounds

In a further aspect of the inventive subject matter, contemplated compounds, libraries, and library compounds will generally have a structure according to **Formula 3**



Formula 3

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2'-beta-methylribofuranose; wherein X is H, alkyl (optionally substituted), CN, C(R')NR"R'", C(O)OR", or NR"R'"; wherein Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'" ; wherein Z is H, NH_2, NHC(O)R", NHNHC(O)R", NHNHC(S)R", or $NHS(O)_2R$", and in which R' is O, NH, NOH, or S, and R" and R'" are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl (all of which may be optionally substituted).

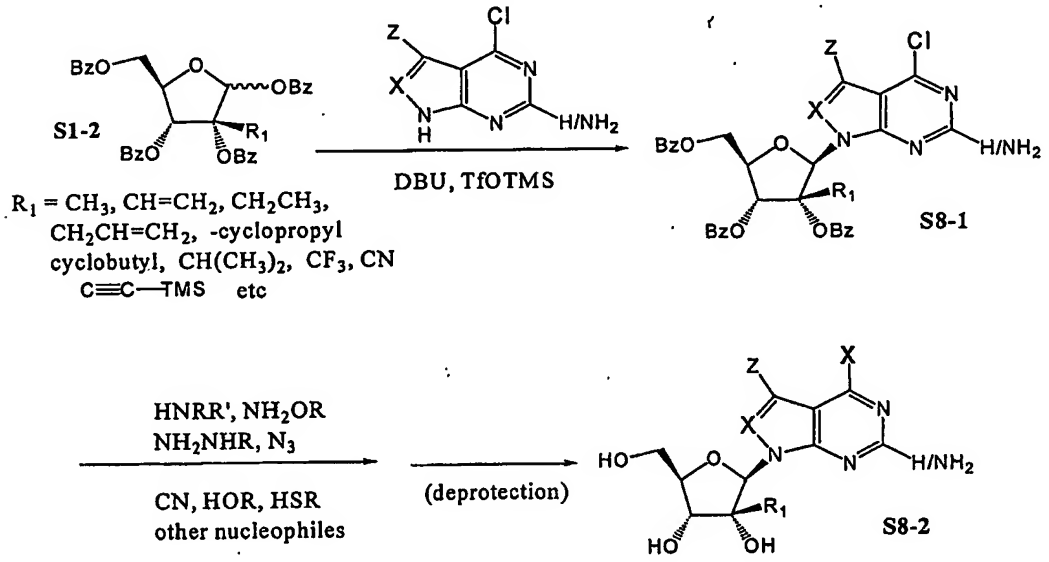
As already discussed above, particularly preferred sugars include a ribofuranose in D- or L-configuration, which may in some aspects be further substituted in one or more positions. For example, where the nucleoside analog is employed as a substrate or cosubstrate for an enzyme using nucleotides, contemplated 7-deaza-8-azapurine nucleosides may include a phosphate group (or phosphate analog, including phosphonate, phosphoamidate, or thiophosphate) coupled to the C5'-position. Depending on the particular location of the enzyme, the charge of the phosphate group may be masked by chemical modification to facilitate penetration of contemplated compounds across a cell membrane, and suitable modifications include esterification (*e.g.*, pivaloyl ester, or S-acyl-esters), amidation, ether formation, etc. In especially preferred modifications, at least part of the modification is cleaved from the compound once the compound enters a cell (*infra*).

In another example, it is contemplated that sugar modifications may be employed to provide improved biochemical properties to contemplated compounds. For example, where the compound is employed as an inhibitor of an RNA-dependent RNA polymerase (*e.g.*, NS5B of HCV), a 2'-beta (and especially a 2'-beta methyl or 2'-beta hydroxymethyl) modification may be included to improve antiviral activity. While not wishing to be bound to a particular theory, it is contemplated that such modification improves the selectivity of contemplated compounds to the HCV polymerase (over other polymerases) as well as decreases the Km of the compound (as compared to the same compound without the modification).

In still further contemplated modifications at the sugar, it should be recognized that all modifications may be employed to increase one or more pharmacological (*e.g.*, half-life time, absorption, bioconversion, etc.) or biochemical parameters (*e.g.*, solubility, electrical charge, selectivity to a structure interacting with contemplated compounds, etc.) of contemplated

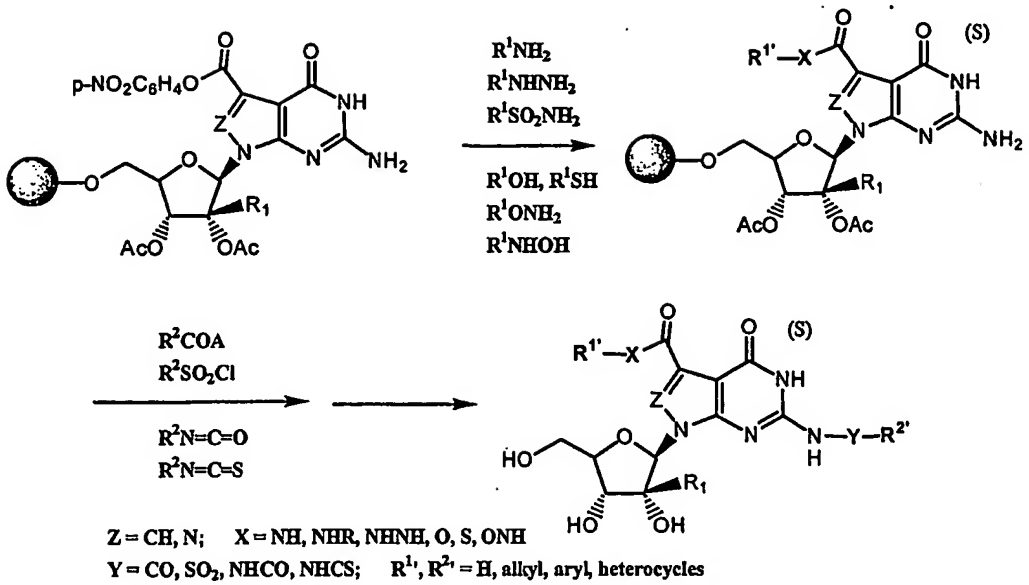
compounds, and all known modifications are contemplated suitable for use herein. Similarly, it should be recognized that the heterocyclic base may also be modified to increase one or more pharmacological or biochemical parameters of contemplated compounds. For example suitable modifications on OH groups may include esterifications and modifications on NH2 groups may include amidations.

The inventors discovered that contemplated 7-deaza-8-azanucleosides may be prepared following various routes, and one exemplary route is depicted in **Scheme 18** below. Here, a suitably modified and protected sugar is first coupled to a 7-deaza-8-azapurine heterocyclic base to yield the corresponding 7deaza-8-azanucleoside, which is then modified to the desired compound(s). Alternatively, as shown in **Scheme 19** below, an appropriately protected precursor nucleoside is coupled to a solid phase and then derivatized in one or more reactions to yield the desired C_2'-substituted 7-deaza-8-azapurine nucleoside(s).



R_1 = CH_3, $CH{=}CH_2$, CH_2CH_3, $CH_2CH{=}CH_2$, -cyclopropyl cyclobutyl, $CH(CH_3)_2$, CF_3, CN C≡C—TMS etc

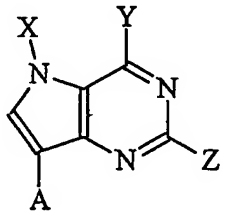
Scheme 18



Scheme 19

9-Deazapurine Nucleoside Libraries and Compounds

In a still further aspect of the inventive subject matter, contemplated compounds, libraries, and library compounds will generally have a structure according to **Formula 4**



Formula 4

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2'-beta-methylribofuranose; wherein X is H, alkyl (optionally substituted), CN, C(R')NR"R'", C(O)OR", or NR"R'"; wherein Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'" ; wherein Z is H, NH_2, NHC(O)R", NHNHC(O)R", NHNHC(S)R", or $NHS(O)_2R$", and in which R' is O, NH, NOH, or S, and R" and R'" are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl (all of which may be optionally substituted).

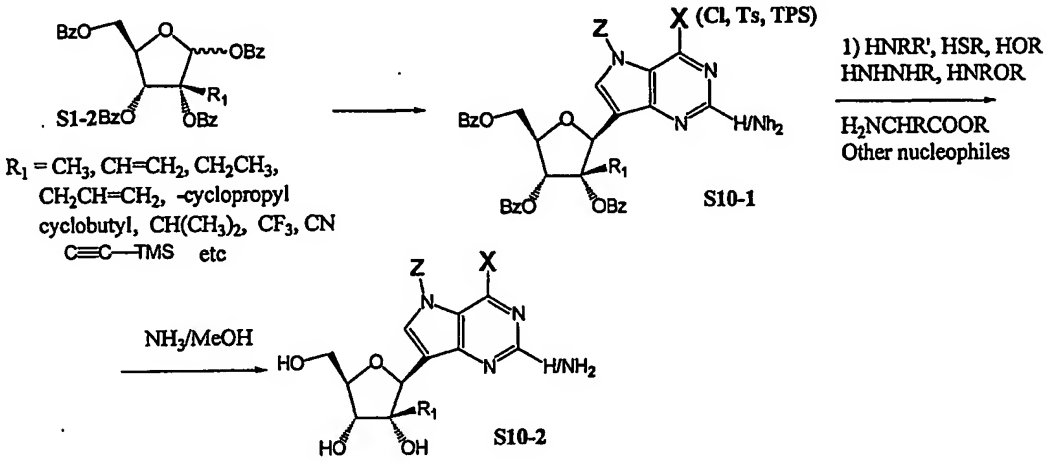
Again, as already discussed above, particularly preferred sugars include a ribofuranose in D- or L-configuration, which may in some aspects be further substituted in one or more positions. For example, where the nucleoside analog is employed as a substrate or cosubstrate for an enzyme using nucleotides, contemplated 9-deazapurine nucleosides may include a phosphate group (or phosphate analog, including phosphonate, phosphoamidate, or thiophosphate) coupled to the C5'-position. Depending on the particular location of the enzyme, the charge of the phosphate group may be masked by chemical modification to facilitate penetration of contemplated compounds across a cell membrane, and suitable modifications include esterification (*e.g.*, pivaloyl ester, or S-acyl-esters), amidation, ether formation, etc. In especially preferred modifications, at least part of the modification is cleaved from the compound once the compound enters a cell (*infra*).

In another example, it is contemplated that sugar modifications may be employed to provide improved biochemical properties to contemplated compounds. For example, where the compound is employed as an inhibitor of an RNA-dependent RNA polymerase (*e.g.*, NS5B of HCV), a 2'-beta (and especially a 2'-beta methyl or 2'-beta hydroxymethyl) modification may be included to improve antiviral activity. While not wishing to be bound to a particular theory, it is contemplated that such modification improves the selectivity of contemplated compounds to the HCV polymerase (over other polymerases) as well as decreases the Km of the compound (as compared to the same compound without the modification).

In still further contemplated modifications at the sugar, it should be recognized that all modifications may be employed to increase one or more pharmacological (*e.g.*, half-life time, absorption, bioconversion, etc.) or biochemical parameters (*e.g.*, solubility, electrical charge, selectivity to a structure interacting with contemplated compounds, etc.) of contemplated compounds, and all known modifications are contemplated suitable for use herein. Similarly, it should be recognized that the heterocyclic base may also be modified to increase one or more pharmacological or biochemical parameters of contemplated compounds. For example suitable modifications on OH groups may include esterifications and modifications on NH_2 groups may include amidations.

The inventors discovered that contemplated 9-deazanucleosides may be prepared following various routes, and one exemplary route is depicted in **Scheme 20** below. Here, a

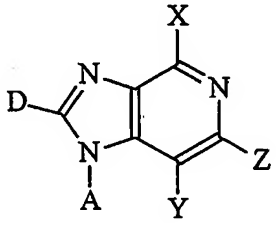
suitably modified and protected sugar is first coupled to an optionally substituted 9-deazapurine heterocyclic base having a leaving group at 6-position, which is then modified to the desired compound(s) in one or more subsequent reactions. This strategy may also be applied to a solid phase approach for synthesis of corresponding libraries.



Scheme 20

3-Deazapurine Nucleoside Libraries and Compounds

In yet another aspect of the inventive subject matter, contemplated compounds, libraries, and library compounds will generally have a structure according to **Formula 5**



Formula 5

wherein A is a sugar or modified sugar in D- or L-configuration, and most preferably a 2',3'-beta-dimethylribofuranose; wherein D is H, halogen, or alkyl, alkenyl, alkynyl, aryl (all of which may be substituted); wherein Y is H, alkyl, alkenyl, alkynyl, aryl (all of which may be optionally substituted); wherein X is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'" ; wherein Z is H or NH_2, and in which R' is O, NH, NOH, or S, and R" and

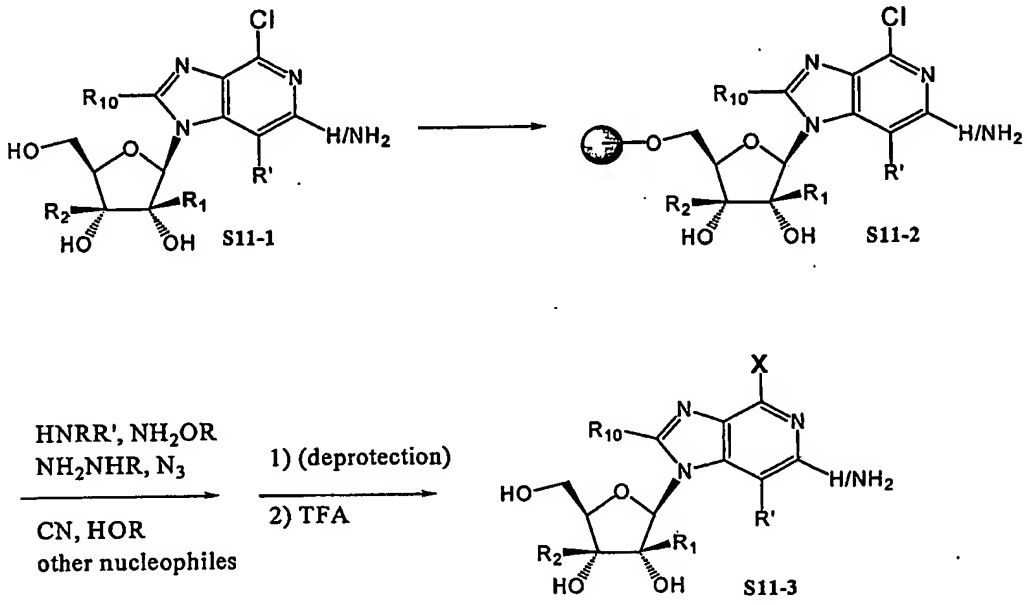
R''' are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl (all of which may be optionally substituted).

Once more, as already discussed above, particularly preferred sugars include a ribofuranose in D- or L-configuration, which may in some aspects be further substituted in one or more positions. For example, where the nucleoside analog is employed as a substrate or cosubstrate for an enzyme using nucleotides, contemplated 9-deazapurine nucleosides may include a phosphate group (or phosphate analog, including phosphonate, phosphoamidate, or thiophosphate) coupled to the C5'-position. Depending on the particular location of the enzyme, the charge of the phosphate group may be masked by chemical modification to facilitate penetration of contemplated compounds across a cell membrane, and suitable modifications include esterification (*e.g.*, pivaloyl ester, or S-acyl-esters), amidation, ether formation, etc. In especially preferred modifications, at least part of the modification is cleaved from the compound once the compound enters a cell (*infra*).

In another example, it is contemplated that sugar modifications may be employed to provide improved biochemical properties to contemplated compounds. For example, where the compound is employed as an inhibitor of an RNA-dependent RNA polymerase (*e.g.*, NS5B of HCV), a 2'-beta (and especially a 2'-beta methyl or 2'-beta hydroxymethyl) modification may be included to improve antiviral activity. While not wishing to be bound to a particular theory, it is contemplated that such modification improves the selectivity of contemplated compounds to the HCV polymerase (over other polymerases) as well as decreases the Km of the compound (as compared to the same compound without the modification).

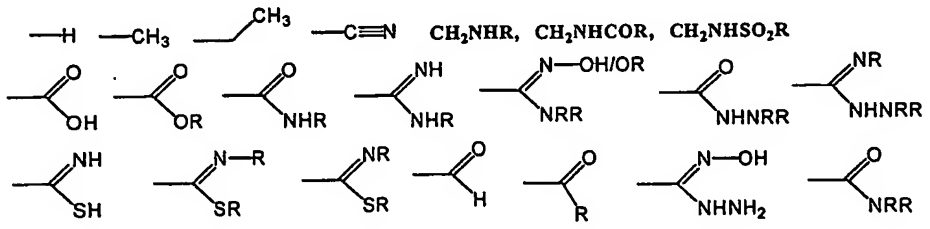
In still further contemplated modifications at the sugar, it should be recognized that all modifications may be employed to increase one or more pharmacological (*e.g.*, half-life time, absorption, bioconversion, etc.) or biochemical parameters (*e.g.*, solubility, electrical charge, selectivity to a structure interacting with contemplated compounds, etc.) of contemplated compounds, and all known modifications are contemplated suitable for use herein. Similarly, it should be recognized that the heterocyclic base may also be modified to increase one or more pharmacological or biochemical parameters of contemplated compounds. For example suitable modifications on OH groups may include esterifications and modifications on NH_2 groups may include amidations.

The inventors discovered that contemplated 9-deazanucleosides may be prepared following various routes, and one exemplary route is depicted in **Scheme 21** below. Here, a suitably modified C_2',C_3'-disubstituted-3-deazanuceloside is coupled to a solid phase under conditions substantially identical to those described in Scheme 21 above, and is then modified to the desired compound(s) in one or more subsequent reactions using procedures substantially identical to the corresponding nucleophilic substitution reactions discussed above.



Scheme 21

It is generally still further contemplated that alternative substituents for radicals X and Y in Formulae 1-5 also independently include the following:

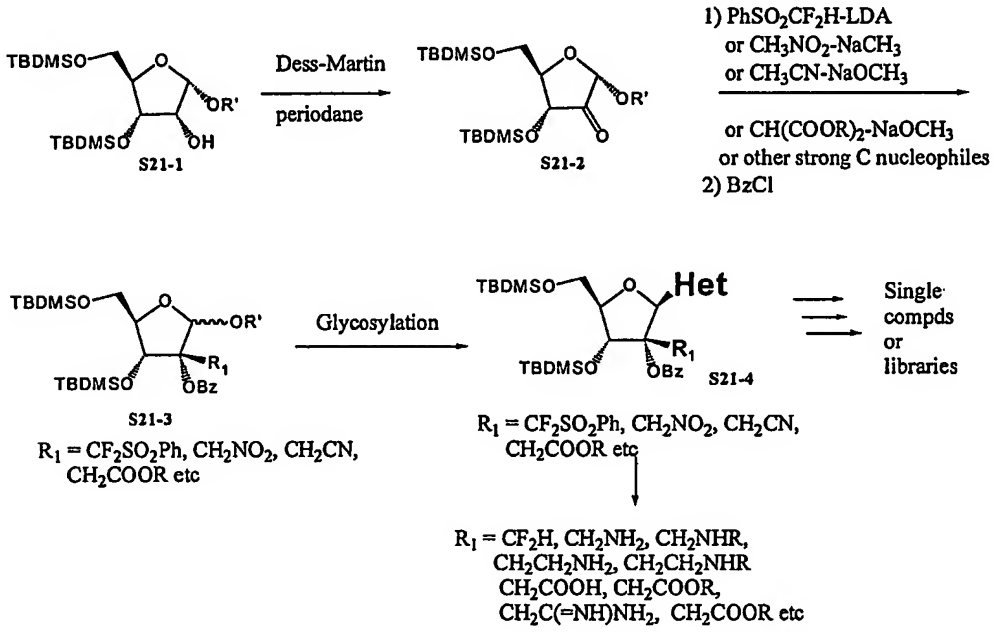


wherein R is alkyl, alkenyl, alkynyl, and aryl, all of which may further be substituted with one or more substituents.

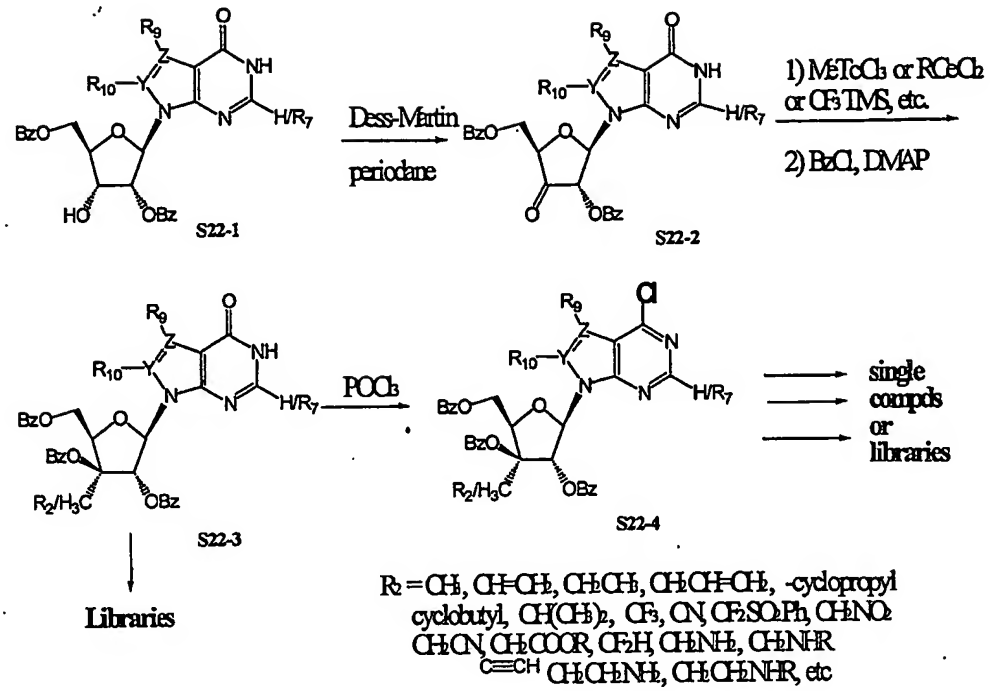
Modification Of The Sugar To Yield C_2'- And/Or C_3'-Substituted Sugars

It is generally contemplated that all known procedures and synthetic schemes for modification of a sugar to yield a C_2'- and/or C_3'-substituted sugar are suitable for use herein, and exemplary protocols may be found in "Modern Methods in Carbohydrate Synthesis" by Shaheer H. Khan (Gordon & Breach Science Pub; ISBN: 3718659212), in U.S. Pat Nos. 4,880,782 and 3,817,982, in WO88/00050, or in EP199,451.

It should further be appreciated that the modification on the sugar portion of a nucleoside may be introduced when the sugar is covalently coupled to the heterocyclic base, or before coupling of the sugar to the heterocyclic base. Exemplary methods of introducing a substituent into the C_2'- or C_3'-position is depicted in **Schemes 22** and **23** below.

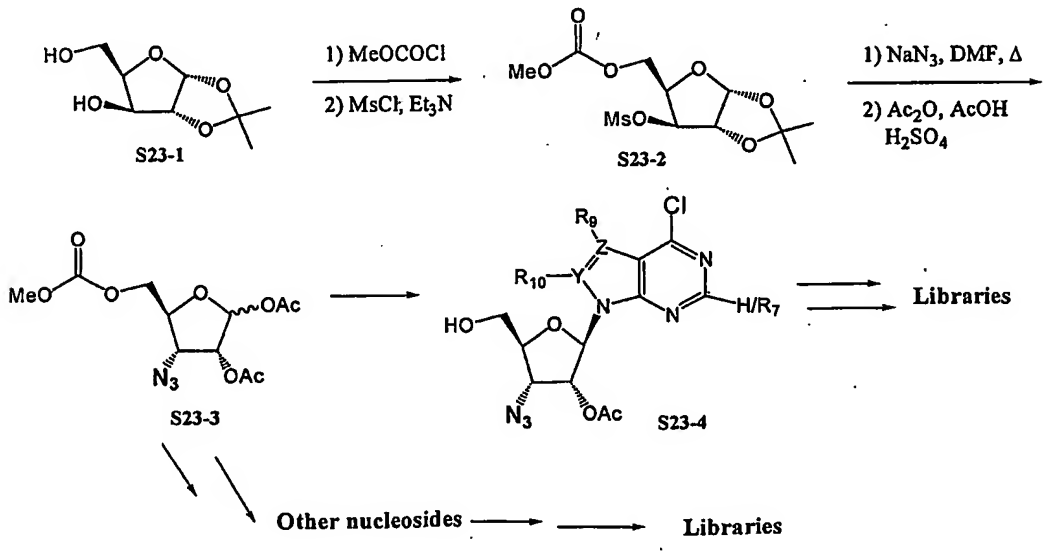


Scheme 21



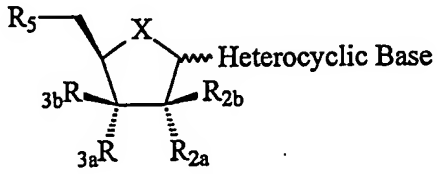
Scheme 22

Similarly, where azido sugars are desired, the azido group may be introduced via the corresponding azido salt in a reaction with a suitable protected sugar as shown in **Scheme 24** below.



Scheme 24

Thus, especially preferred alternative sugars for contemplated nucleosides include those having the general **Formula 6**



Formula 6

wherein Heterocyclic Base is any one of the heterocyclic bases contemplated herein; X is O, S, or CH_2, R_{2a} and R_{3a} are independently H, OH, SH, NH_2, NHR, OR, SR, CH_2OH, N_3, NH_2, COOH, halogen, or $P(O)(OR)_2$ with R being alkyl, acyl, or alkenyl (each of which may optionally be substituted); R_{2b} and R_{3b} are independently H, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2(CH_2)_{2\text{-}5}CH_3$, C_1-C_8 alkyl, alkenyl, or alkynyl (which may be linear, branched, or cyclic), C_5-C_{12}-aromatic or heterocyclic system, halogen (*i.e.*, F, Cl, Br, I), CF_3, CHF_2, CCl_3, $CHCl_2$, CH_2Cl, CH_2OH, CN, CH_2CN, CH_2NH_2, CH_2NHR, CH_2OR, CHO, CH_2COR, N_3, or NH_2, SH, NH_2, NHR, OR, SR, CH_2OH, N_3, NH_2, COOH, halogen, or $P(O)(OR)_2$ with R being alkyl, acyl, or alkenyl (each of which may optionally be substituted), and wherein R_5 is OH, monophosphate, diphosphate, triphosphate, or analogs thereof (*e.g.*, phosphonate, boranophosphate, or thiophosphate).

Contemplated Prodrugs and Metabolites

It should still further be appreciated that the compounds according to the inventive subject matter also include prodrug forms, phosphorylated forms (most preferably at the C5'-atom) and/or metabolites. Particularly suitable prodrug forms of contemplated compounds may include a moiety that is covalently coupled to at least one of the C2'-atom, C3'-atom, and C5'-atom, thereby replacing the OH group at the at least one of the C2'-atom, C3'-atom, and C5'-atom, wherein the moiety is preferentially cleaved from the compound in a target cell (*e.g.*, Hepatocyte) or a target organ (*e.g.*, liver). While not limiting to the inventive subject matter, it is preferred that cleavage of the prodrug into the active form of the drug is mediated (at least in part) by a cellular enzyme, particularly receptor, transporter, and cytochrome-associated enzyme systems (*e.g.*, CYP-system).

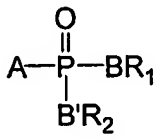
Especially contemplated prodrugs comprise a cyclic phosphate, cyclic phosphonate and/or a cyclic phosphoamidate, which are preferentially cleaved in a hepatocyte to produce the corresponding nucleotides. There are numerous such prodrugs known in the art, and all of those are considered suitable for use herein. However, especially contemplated prodrug forms are disclosed in WO 01/47935 (Novel Bisamidate Phosphonate Prodrugs), WO 01/18013 (Prodrugs For Liver Specific Drug Delivery), WO 00/52015 (Novel Phosphorus-Containing Prodrugs), and WO 99/45016 (Novel Prodrugs For Phosphorus-Containing Compounds), all of which are incorporated by reference herein. Consequently, especially suitable prodrug forms include those targeting a hepatocyte or the liver.

Still further particularly preferred prodrugs include those described by Renze et al. in Nucleosides Nucleotides Nucleic Acids 2001 Apr-Jul;20(4-7):931-4, by Balzarini et al. in Mol Pharmacol 2000 Nov;58(5):928-35, or in U.S. Pat. No. 6,312,662 to Erion et al., U.S. Pat. No. 6,271,212 to Chu et al., U.S. Pat. No. 6,207,648 to Chen et al., U.S. Pat. No. 6,166,089 and U.S. Pat. No. 6,077,837 to Kozak, U.S. Pat. No. 5,728,684 to Chen, and published U.S. Application with the number 20020052345 to Erion, all of which are incorporated by reference herein. Alternative contemplated prodrugs include those comprising a phosphate and/or phosphonate non-cyclic ester (SATE ester, pivaloyl ester, etc.), and an exemplary collection of suitable prodrugs is described in U.S. Pat. No. 6,339,154 to Shepard et al., U.S. Pat. No. 6,352,991 to Zemlicka et al., and U.S. Pat. No. 6,348,587 to Schinazi et al. Still further particularly contemplated prodrug forms are described in FASEB J. 2000 Sep;14(12):1784-92, Pharm. Res. 1999, Aug 16:8 1179-1185, and Antimicrob Agents Chemother 2000, Mar 44:3 477-483, all of which are incorporated by reference herein.

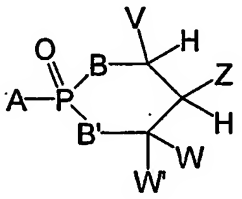
Thus, particularly preferred prodrug forms will comprise a moiety covalently coupled to at least one of the C2'-atom, C3'-atom, and C5'-atom, wherein at least part of the moiety is preferentially cleaved from the compound in a target cell or target organ. As used herein, the term "preferentially cleaved...in a target cell or target organ" means that cleavage occurs in a particular target cell or target organ at a rate that is at least 3 times, more typically at least 10 times, and most typically at least 50 times higher than in a non-target cell or non-target organ. The term "target cell" or "target organ" as used herein refers to a cell or organ that is infected with a virus, and especially includes a hepatocyte infected with an HCV virus. Cleavage may be mediated by enzymes (but also by non-enzymatic processes, *e.g.*, via reductive cleavage), and it is particularly preferred that enzymatic cleavage is mediated by a liver-specific enzyme

system (*e.g.*, CYP system). Consequently, it should be appreciated that certain prodrug forms of contemplated compounds may be cleaved in a target cell and/or target organ to provide a nucleotide analog. Alternatively, prodrugs may also be converted to the corresponding nucleoside (*e.g.*, where the moiety does not include a phosphorus atom).

An exemplary preferred prodrug of contemplated compounds may therefore include a moiety according to **Formula M1** or **M2** (covalently coupled to the compound, typically to the C5'-atom, C2'-atom, and/or C3'-atom)



M1



M2

wherein A in M1 or M2 is O or CH_2 and replaces the 5'-OH group of the compound of Formulae 1 -5; B and B' are independently O or NH, and where B is NH then R_1 or R_2 is an amino acid that forms a peptide bond with the N atom of the NH; and R_1, R_2, V, W, and W' are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkaryl, each of which is optionally substituted, and Z is hydrogen, CHWOH, CHWOCOW', SW, or CH_2aryl. Especially preferred compounds according to Formula M2 are those in which in A is O or CH_2, B and B' are independently O or NH, and in which Z, W, and W' are H and V is m-Chlorophenyl.

With respect to metabolites of contemplated compounds, it should be recognized that all metabolites that have a desirable therapeutic effect and especially an antiviral effect, are deemed suitable. Consequently, particularly suitable metabolites will generally include 5'-phosphates (*e.g.*, monophosphate, diphosphate, and/or triphosphate esters), which may or may not be generated by an enzyme (*e.g.*, kinase, oxidase). Further metabolites include those that are generated via enzymatic action on the heterocyclic base (*e.g.*, via deaminase, deamidase, or hydroxylase).

Use of Contemplated Compounds

It is generally contemplated that all libraries will comprise one or more nucleosides that have numerous biological activities, and especially contemplated biological activities include *in vitro* and *in vivo* inhibition of DNA and/or RNA polymerases, reverse transcriptases, and ligases. Therefore, contemplated nucleosides will exhibit particular usefulness as *in vitro* and/or *in vivo* antiviral agents, antineoplastic agents and immunomodulatory agents.

Particularly contemplated antiviral activities include at least partial reduction of viral titers of respiratory syncytial virus (RSV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex type 1 and 2, herpes genitalis, herpes keratitis, herpes encephalitis, herpes zoster, human immunodeficiency virus (HIV), influenza A virus, Hanta virus (hemorrhagic fever), human papilloma virus (HPV), yellow fever virus, and measles virus. The anti-HCV activity of the nucleosides and libraries were tested by Replicon and BVDV cell-line based assays. The HCV NS5B polymerase activity was tested for the mono-, di- and triphosphates of the nucleosides or 5'-methylenephospnonate derivatives. The compounds and libraries were tested for their replication of Hepatitis C virus RNA by cell-line based HCV Replicon assay as described in V. Lohmann, F. Korner, J.-O. Koch, U. Herian, L. Theilmann, R. Bartenschlager, "Replication of a Subgenomic Hepatitis C virus RNAs in a Hepatoma Cell Line", Sciences, 1999, *285*, 110. Especially contemplated immunomodulatory activity includes at least partial reduction of clinical symptoms and signs in arthritis, psoriasis, inflammatory bowel disease, juvenile diabetes, lupus, multiple sclerosis, gout and gouty arthritis, rheumatoid arthritis, rejection of transplantation, giant cell arteritis, allergy and asthma, but also modulation of some portion of a mammal's immune system, and especially modulation of cytokine profiles of Type 1 and Type 2. Where modulation of Type 1 and Type 2 cytokines occurs, it is contemplated that the modulation may include suppression of both Type 1 and Type 2, suppression of Type 1 and stimulation of Type 2, or suppression of Type 2 and stimulation of Type 1.

Where contemplated nucleosides are administered in a pharmacological composition, it is contemplated that suitable nucleosides can be formulated in admixture with a pharmaceutically acceptable carrier. For example, contemplated nucleosides can be administered orally as pharmacologically acceptable salts, or intravenously in a physiological

saline solution (*e.g.*, buffered to a pH of about 7.2 to 7.5). Conventional buffers such as phosphates, bicarbonates or citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration. In particular, contemplated nucleosides may be modified to render them more soluble in water or other vehicle, which for example, may be easily accomplished with minor modifications (salt formulation, esterification, *etc.*) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient.

In certain pharmaceutical dosage forms, prodrug forms of contemplated nucleosides may be formed for various puposes, including reduction of toxicity, increasing the organ or target cell specificity, etc. Among various prodrug forms, acylated (acetylated or other) derivatives, pyridine esters and various salt forms of the present compounds are preferred. One of ordinary skill in the art will recognize how to readily modify the present compounds to pro-drug forms to facilitate delivery of active compounds to a target site within the host organism or patient. One of ordinary skill in the art will also take advantage of favorable pharmacokinetic parameters of the pro-drug forms, where applicable, in delivering the present compounds to a targeted site within the host organism or patient to maximize the intended effect of the compound.

In addition, contemplated compounds may be administered alone or in combination with other agents for the treatment of various diseases or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the present invention or a functional derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered separately or together and when administered separately this may occur simultaneously or separately in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Experiments and Data

SYNTHESIS OF EXEMPLARY COMPOUNDS

Scheme 1

4-Amino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **2.** A solution of 8 - bromo-4-amino-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-d]-pyrimidine-5-carbonitrile 1 (5.5g, 8.06 mmol) in dioxane (50 ml) and NEt_3 (2.25 ml, 16.12 mmol) was shaken well under H_2 atmosphere (30 psi) in presence of Pd / C (10% w / w, 500 mg) for 16h at room temperature. The reaction mixture filtered over a celite bed and washed with dioxane (2 x 50 ml). The filtrate evaporated to obtain the crude 4-amino-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile in quantitative yield (4.8g). This benzoate was then treated with saturated methanolic ammonia (100 ml) at room temperature for 16h. The volatiles evaporated and the residue was purified over flash silica gel chromatography (fsgc) to obtain the title product (2.0g, 85% yield for two steps).

4-Oxo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **3.** To a solution of 4-amino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **2** (2.0g, 6.87 mmol) in water (40ml) and acetic acid (10 ml), $NaNO_2$ (4.74 g, 68.7 mmol) was added and the reaction mixture heated at 70°C for 1h. The volatiles were evaporated and the residue was co-evaporated with pyridine (2 x 50ml). The residue was resuspended in pyridine (50ml) and then treated with acetic anhydride (5 ml, 53 mmol). After 16 h at room temperature MeOH (25 ml) was added and the volatiles were evaporated. The residue obtained was redissolved in water (100 ml) and CH_2Cl_2 (300 ml). The organic layer was separated and washed with water (200 ml) and brine (200 ml), dried (Na_2SO_4) and evaporated. The crude residue was then purified over fsgc to obtain the title product (2.1g, 73% yield for 2 steps).

4-Chloro-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **4.** A solution of 4-oxo-7- (2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **3** (2.1g, 5.02 mmol) in $POCl_3$ (20 ml) was refluxed for 1h. The reaction mixture was allowed to attain room temperature and the volatiles evaporated. The residue obtained was dissolved in CH_2Cl_2 (150 mL) and the organic layer was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated. The residue was dried

over P_2O_5 for 16h under vacuum to obtain the crude 4-chloro-7-(2,3,5-tri-*O*-acetyl -β-D-ribofuranosyl)pyrrolo[2,3-d]-pyrimidine-5-carbonitrile (1.9 g) which was carried forward for the next reaction without purification.

4-*N,N*-Dimethylamino-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **5.** A solution of 4-chloro-7-(2,3,5-tri-*O*-acetyl -β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile (1.2 g, 2.745 mmol) in MeOH (20 mL) was treated with a solution of dimethylamine in MeOH (10 mL). The reaction mixture was refluxed for 16h and the volatiles were evaporated. The residue obtained was suspended in MeOH (10 mL) and the white solids separated were filtered and washed with cold MeOH (2 x 5 mL) to obtain the title compound which was dried over P_2O_5 for 16 h under vacuum (0.4 g, 46%). ^{1}H NMR (300 MHz, CD_3OD) δ: 8.34 (s), 8.24 (s), 6.13 (d, J = 5.1 Hz), 4.52 (t, 1H), 4.27 (dd, 1H), 4.12 (dd, 1H), 3.82 (ddd, 2H), 3.18 (s, 6H).

4-*N,N*-Dimethyl-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-*N*-hydroxycarbamidine **6.** A solution of 4-*N,N*-dimethyl-amino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.1 g, 0.31 mmol) in ethyl alcohol (10 mL) was treated with an aqueous solution (0.2 mL, 3.1 mmol, 50% w/v) of hydroxylamine. The reaction mixture was refluxed for 16 h at 85 °C. The volatiles evaporated and the residue was purified by flash silica gel chromatography to obtain the pure title product as a white solid (0.075 mg, 68%). ^{1}H NMR (300 MHz, CD_3OD) δ: 8.15 (s), 7.58 (s), 6.07 (d, J = 6.0 Hz), 4.59 (dd, 1H), 4.26 (dd, 1H), 4.09 (dd, 1H), 3.78 (ddd, 2H), 3.18 (s, 6H).

4-S-Methyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile **7.** A solution of 4-chloro-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.5 g, 1.14 mmol) in THF (20 mL) was treated with NaSMe (0.096 g, 1.37 mmol). The reaction mixture was refluxed for 1h and the volatiles were evaporated. The residue obtained was suspended in MeOH (10 mL) and treated with NaCN (0.1 g, 2.04 mmol). The reaction mixture was stirred at room temperature for 16 h. The volatiles evaporated and the residue was purified by flash silica gel chromatography to obtain the pure title product as a white solid (0.2 g, 54%). ^{1}H NMR (300 MHz, CD_3OD) δ: 8.68 (s), 8.45 (s), 6.23 (d, J = 5.4 Hz), 4.51 (t, 1H), 4.29 (dd, 1H), 4.12(dd, 1H), 3.82 (ddd, 2H), 2.72 (s, 3H).

4-S-Methyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-N-hydroxy-carbamidine **8.** A solution of 4-S-methyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.15 g, 0.46 mmol) in isopropyl alcohol (15 mL) was treated with an aqueous solution (0.3 mL, 4.65 mmol, 50% w/v) of hydroxylamine. The reaction mixture refluxed for 16 h at 85 °C. The volatiles evaporated and the residue was dissolved in minimum MeOH (2 mL) and kept away for 16h to obtain the pure title product as a white solid (0.1 g, 64%) which was filtered and washed with cold MeOH. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.57 (s), 7.81 (s), 6.21 (d, J = 5.4 Hz), 4.56 (dd, 1H), 4.29 (m, 1H), 4.09(m, 1H), 3.78 (ddd, 2H), 2.62 (s, 3H).

Scheme 2

4-*N*-Methylamino-7-(5-*O*-acetyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine-5-carbonitrile **9.** A solution of 4-chloro-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]-pyrimidine-5-carbonitrile (0.5 g, 1.15 mmol) in THF (10 mL) was treated with a solution of methylamine in THF (5 mL, 2N). The reaction mixture was stirred for 16h at room temperature and the volatiles were evaporated. The residue was purified by flash silica gel chromatography to obtain the pure title product as a white solid (0.25 g, 63%). ^{1}H NMR (300 MHz, CD_3OD) δ: 8.28 (s), 8.07 (s), 6.15 (d, J = 4.5 Hz), 4.48 (dd, 1H), 4.36 (dd, 2H), 4.25 (m, 2H), 3.12 (s, 3H), 2.10 (s, 3H).

4-*N*-Methylamino-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-*N*-hydroxy-carbamidine **10** and 4-*N*-Methylamino-7-(5-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-*N*-hydroxy-carbamidine **11.** A solution of 4-*N*-methyl-7-(5-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.14 g, 0.4 mmol) in isopropyl alcohol (10 mL) was treated with an aqueous solution (0.26 mL, 4.0 mmol, 50% w/v) of hydroxylamine. The reaction mixture was refluxed for 16 h at 85 °C. The volatiles evaporated and the residue was purified by flash silica gel chromatography to obtain the pure title product as a white solid (0.080 g, 62%) and 4-*N*-methylamino-7-(5-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-*N*-hydroxycarbamidine **11** (0.05 g, 38%) was also isolated from the reaction mixture. ^{1}H NMR of **12** (300 MHz, CD_3OD) δ: 8.07 (s), 7.68 (s), 6.17 (d, J = 6.3 Hz), 4.61 (dd, 1H), 4.26 (dd, 2H), 4.10 (dd, 2H), 3.80 (ddd, 2H), 3.02 (s, 3H).

^{1}H NMR of **11** (300 MHz, CD_3OD) δ: 8.10 (s), 7.68 (s), 6.17 (d, J = 4.2 Hz), 4.44-4.19 (m, 5H), 3.03 (s, 3H), 2.08 (s, 3H).

Scheme 3

4-Methoxy-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile **12** and 4-(N_1-Methyl)hydrazino-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile **13.** Compound 4 (2.0 g, 4.59 mmol) was allowed to stir with *N',N'*-dimethyl hydrazine (2.5 ml) in MeOH (20 ml) at room temperature for 2 days. The reaction mixture was evaporated to dryness and treated with $MeOH/NH_3$. The resulting solution was stirred for 12 h at RT and evaporated to dryness. The residue was purified by flash chromatography over silica gel using $CHCl_3 \rightarrow$ MeOH as the eluent. Two fractions were isolated. The fast moving product was identified as **12** and the slow moving product identified as **13**; yield of **12**: 1.0 g (71%); ^{1}H NMR (Me_2SO-d_6) δ: 3.60 (m, 2H, $C_{5'}H$), 3.92 (m, 1H, $C_{4'}H$), 4.10 (m, 4H, $C_{3'}H$ & OCH_3), 4.38 (m, 1H), 5.12 (t, 1H, $C_{5'}OH$), 5.22 (d, 1H, O*H*), 5.50 (d, 1H, O*H*), 6.14 (d, 1H, J = 5.7 Hz, $C_{1'}H$), 8.57 (s, 1H, C_6H), 8.63 (s, 1H, C_2H); yield of **13**: 0.4 g (27%); ^{1}H NMR (Me_2SO-d_6) δ: 3.34 (s, 3H, CH_3), 3.60 (m, 2H, $C_{5'}H$), 3.90 (m, 1H, $C_{4'}H$), 4.08 (m, 1H, $C_{3'}H$), 4.08 (m, 1H), 4.34 (m, 1H), 5.10 – 5.20 (m, 4H, $C_{5'}OH$, O*H* & NH_2), 5.40 (d, 1H, O*H*), 6.09 (d, 1H, J = 5.7 Hz, $C_{1'}H$), 8.15 (s, 1H, C_6H), 8.35 (s, 1H, C_2H).

4-Hydroxyamino-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide oxime **14.** A mixture of compound **12** (0.30 g, 0.98 mmol) and aqueous hydroxylamine (20 ml) in MeOH (20 ml) was heated at reflux for 12 h. The reaction mixture was cooled and the precipitated solid was filtered and dried to give 100 mg (30%) of **14** as colorless crystals; ^{1}H NMR (Me_2SO-d_6) δ: 3.58 (m, 2H, $C_{5'}H$), 3.86 (m, 1H, $C_{4'}H$), 4.07 (m, 1H), 4.30 (m, 1H), 5.08 (m, 2H, $C_{5'}OH$ & O*H*), 5.32 (m, 1H, O*H*), 6.04 (m, 2H, $C_{1'}H$), 7.86 (s, 1H, C_6H), 8.15 (s, 1H, C_2H), 9.03 (m, 1H), 9.74 (m, 1H), 11.85 (m, 1H).

Scheme 4

3,4-Dihydro-4-oxo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile **3** and Methyl 3,4-Dihydro-4-oxo-7-(2,3;5-tri-O-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxylate **15.** 4-Amino-3-cyano-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine **2** (A. R. Porcari and L. B. Townsend,

Nucleosides & Nucleotides, 18(2), 153-159 (1999)) (15.0 g, 24.88 mmol) was allowed to stir with methanolic ammonia (saturated at 0°C, 400 ml) in a steel bomb for 12 h at room temperature. The steel vessel was cooled to 0 °C, opened carefully and the contents evaporated to dryness. The residue was triturated with EtOAc (100 ml) and filtrated. To the stirred solution of the residue (7.0 g) in acetic acid (100 ml) and water (200 ml) at 50 °C was added $NaNO_2$ (16.5 g) in small portions during a 1h period. After the addition of $NaNO_2$, the temperature of the reaction mixture was raised to 70 °C and stirred at that temperature for 1 h. The reaction mixture was evaporated to dryness and the residue was co-evaporated with dry pyridine (2 x 150 ml) and used as such for the next reaction.

The above residue was suspended in dry pyridine (150 ml) and dry DMF (100 ml) mixture. To this stirred mixture was added acetic anhydride (30.6 g, 300 mmol) during a 30 min period. The reaction mixture was stirred at room temperature for 16 h and evaporated to dryness. The residue was partitioned between EtOAc (300 ml) and sat $NaHCO_3$ (250 ml) solution, and extracted in EtOAc. The organic extract was washed with water (200 ml) and brine (100 ml), dried and evaporated to dryness. The crude product was purified by flash chromatography over silica gel using $CHCl_3$ → acetone as the eluent. Two products were isolated. ^{1}H NMR ($CDCl_3$) δ: 2.02 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 4.20 – 4.40 (m, 3H, $C_5'H$ & $C_4'H$), 5.43 (m, 1H), 5.66 (m, 1H), 6.23 (d, 1H, J = 5.4 Hz, $C_1'H$), 8.11 (s, 2H, C_6H), 8.34 (s, 1H, C_2H), 12.56 (bs, 1H, NH).

Methyl 4-Chloro-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxylate **16.** Compound **15** (2.4 g, 5.32 mmol) was heated at reflux with $POCl_3$ (60 ml) for 6 h. The hot solution was cooled to room temperature and evaporated to 50 ml in volume under reduced pressure. The solution was treated with ice and stirred for 1 h. The aqueous solution was extracted with EtOAc (2 x 100 ml). The organic extract was washed with water (100 ml) and brine (70 ml), dried and evaporated to dryness to give 1.8 g (72%) of a syrup.

Methyl 3,4-Dihydro-4-thio-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-thiocarboxylate **17.** Compound **16** (1.7 g, 3.63 mmol) and Lawesson's reagent (2.0 g) in 1,4-dioxane (60 ml) was heated at reflux for 6 h. TLC showed two spots. Additional Lawesson's reagent (1.0 g) was added and the heating continued for 6 h more. The reaction mixture was evaporated to dryness. The residue was purified by flash

chromatography over silica gel using $CHCl_3 \rightarrow$ EtOAc as the eluent. The fast moving fractions were pooled and concentrated to give 0.90 g (51%) of **17**; ^{1}H NMR ($CDCl_3$) δ: 2.09 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 2.23 (s, 3H, $COCH_3$), 4.31 (s, 3H, OCH_3), 4.38 (m, 2H, $C_{5'}H$), 4.42 (m, 1H, $C_{4'}H$), 5.44 (m, 1H), 5.62 (m, 1H), 6.38 (d, 1H, $C_{1'}H$), 7.94 (s, 2H, C_6H & C_2H), 12.30 (bs, 1H, N*H*).

Methyl 4-Methylthio-7-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-thiocarboxylate **18:** To a stirred solution of **17** (0.60 g, 1.24 mmol) in dry CH_3CN (50 ml) under argon atmosphere was added N,N-diisopropylethylamine (0.26 g, 2.0 mmol) followed by methyl iodide (2.0 ml), and the stirring continued at room temperature for 12 h. The reaction mixture was evaporated to dryness. The residue was purified by flash chromatography over silica gel using $CHCl_3 \rightarrow$ acetone as the eluent. The pure fractions were pooled and concentrated to give 0.45 g (73%) of **33** as foam.

7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxhyrazino hydrazimidine **19:** A mixture of **18** (0.20 g, 0.40 mmol) and hydrazine hydrate (2.0 ml) in EtOH (20 ml) was heated at reflux for 1 day. The reaction mixture was cooled to room temperature with stirring for 6 h. The precipitated solid was filtered and dried to afford 0.018 g (14%) of **19**; ^{1}H NMR (Me_2SO-d_6) δ: 3.58 (m, 2H, $C_{5'}H$), 3.86 (m, 1H, $C_{4'}H$), 4.06 (m, 1H), 4.34 (m, 1H), 4.46 (bs, 2H, NH_2), 5.12 (d, 1H, O*H*), 5.20 (t, 1H, $C_{5'}OH$), 5.34 (m, 1H, O*H*), 5.99 (d, 1H, $C_{1'}H$), 6.58 (bs, 2H, NH_2), 7.54 (s, 1H, C_6H), 7.75 (s, 1H, C_2H), 8.14 (s, 1H), 10.06 (bs, 1H).

Scheme 5

5-Cyano-7-(2′-*C*-methyl-2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo [2,3-d]pyrimidone **21.** 4-Amino-5-cyano-7-(2′-*C*-methyl-2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidone (**20**) (Yasushi Murai, Hironori Shiroto, Tatsuya Ishizaki, Takamasa Limori, Yoshio Kodama, Yasuo Ohtsuka and Takeshi Oishi. *Heterocycles*. 1992, *33 (1)*, 391-404) (155 mg, 0.51 mmol) was dissolved into a mixture of acetic acid and water (10 ml, 1:1). Sodium nitrile (175 mg, 2.5 mmol) was added to the above solution. This mixture was stirred at 70 °C for 1 hour. TLC (CH_2Cl_2-MeOH: 10:1) showed the starting material disappeared. The reaction mixture was evaporated to dryness under vacuum, and the residue was treated with the mixture of acetic anhydride and pyridine (10 ml, 1:1). After stirring for 12 hours at room temperature, the reaction mixture was evaporated

to dryness, and the residue was purified on a silica gel column with chloroform/ethyl acetate (1:1) to yield the desired product as a white solid (130 mg, 60% for two steps); ^{1}H NMR (CD_3OD) δ: 8.05 (s, 1H), 8.00 (s, 1H), 6.56 (s, 1H), 5.48 (d, 1H, J = 6.0 Hz), 4.40 (m, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.38 (s, 3H).

4-Chloro-5-cyano-7-(2′-*C*-methyl-2′,3′,5′-tri-*O*-acetyl-β-D-ribofurano syl)pyrrolo[2,3-d]pyrimidine **22.** Compound **21** (100 mg, 0.23 mmol) was suspended in 5 ml of phosphorus oxychloride and heated to reflux for 30 min. Excess phosphorus oxychloride was removed immediately under vacuum and the remaining residue was dissolved into 15 ml of dichloromethane with a small amount of ice. The organic phase was dried (Na_2SO_4) and evaporated to dryness. This compound was used for the next step directly without any purification.

4-Methylamino-5-cyano-7-(2′-*C*-methyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine **23.** Compound **22** (50 mg, 0.11 mmol) was dissolved in a solution of methylamine in THF (1M, 5 ml), and the reaction mixture was stirred at room temperature for 18 hours. TLC showed the disappearance of starting material and the appearance of a new spot. The mass spectrum of the reaction mixture indicated the formation of the desired compound. The solvent was removed and the residue was treated with methanolic ammonia (5 ml), saturated at 0 °C, and sealed in a pressure bottle, for 18 hours at room temperature. The solvent was removed under vacuum, and the residue was purified from the silica column using a mixture of chloroform/methanol (9:1) as the eluting solvent system. The desired compound was obtained as oil (25 mg, 70% for two steps); ^{1}H NMR (CD_3OD) δ: 8.40 (s, 1H), 8.27 (s, 1H), 6.25 (s, 1H), 4.12-4.05 (m, 3H), 3.86 (dd, 1H, J = 12.6, 2.7 Hz), 3.12 (s, 3H), 0.85 (s, 3H).

4-Methylamino-7-(2′-*C*-methyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide oxime **24.** Compound **23** (15 mg, 0.03 mmol) was dissolved in 10 ml. of isopropanol and hydroxylamine (10 mg) was added. This mixture was heated at 75 °C for 3 hours, cooled to room temperature and evaporated to dryness, and the residue was purified from the silica column using a mixture of chloroform/methanol (9:1) as the eluting solvent system. The desired compound was obtained as white solid. (7 mg, 45%); ^{1}H NMR (CD_3OD) δ 8.11 (s, 1H), 7.80 (s, 1H), 6.23 (s, 1H), 4.11-4.02(m, 3H), 3.88 (dd, 1H, J = 12.6, 3.3 Hz), 3.05 (s, 3H), 0.86 (s, 3H); MS: m/z 352 $[M + H]^+$.

Scheme 6

4-Dimethylamino-7-(2′-*C*-methyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide oxime **26.** Compound **22** (50 mg, 0.11 mmol) was dissolved in a solution of dimethylamine in THF (1M, 5 ml), and the reaction mixture was stirred at room temperature for 18 hours. TLC showed the disappearance of starting material and the appearance of a new spot. The mass spectrum of the reaction mixture indicated the formation of the desired compound. The solvent was removed and the residue was treated with methanolic ammonia (5 ml), saturated at 0 °C, and sealed in a pressure bottle, for 18 hours at room temperature. The solvent was removed under vacuum, and the residue of compound **25** was dissolved in 10 ml of isopropanol and hydroxylamine (10 mg) was added. This mixture was heated at 75 °C for 3 hours, cooled to room temperature and evaporated to dryness. The residue was purified from the silica column (chloroform/methanol = 9:1). The desired compound **26** was obtained as a white solid (16 mg, 39 % for three steps); ^{1}H NMR (CD_3OD) δ8.17 (s, 1H), 7.76 (s, 1H), 6.30 (s, 1H), 4.12 (d, 1H, J= 8.7 Hz), 4.03 (m, 1H), 4.00 (m, 1H), 3.83 (dd, 1H, J= 12.0, 6.0 Hz), 3.19 (s, 6H), 0.87 (s, 3H).

Schemes 7-10

The synthetic protocols for Schemes 7-10 generally follow the corresponding synthetic steps in the protocols as outlined in Schemes 1-6 above.

Scheme 11

Compound **S1-2** was prepared from **S1-1** according to literature procedure (R. E. Harry O'Kuru, J. M. Smith, M. S. Wolfe, J. Org. Chem. 1997, 62, 1754-1759; M. S. Wolfe, R. E. Harry-O'kuru, Tetrahedron Lett. 1995, 36, 7611-7614; and N-S, Li, X.-Q. Tang, J. A. Piccirilli, Org. Lett. 2001, 3, 1025-1028).

Compound **S1-2** was treated with hydrogen bromide and then glycosylated with 6-chloro-7-deazapurine derivatives at the elevated temperature using common glycosylation catalysts. The reaction mixture was worked up and purified to provide 7-deaza-nucleoside **S1-3**. This compound was reacted with amines, hydrozines, hydroxyamines, alcohols, thioalcohols and other nucleophilic building blocks (see exemplary building block lists) in a

parallel way. The resultant compounds were treated with ammonia solution in methanol to provide single compounds **S1-4**.

Scheme 12

The compound **S1-3** was treated with ammonia solution in methanol or NaCN to yield the unprotected compound **S2-1**. A mixture of polystyrene MMT chloride resin, compound **S2-1** (1.5 equiv.) DMP in DMF and pyridine was shaken at room temperature for 24 hours. The resin was filtered and then washed with DMF/pyridine and dichloromethane. The resulted dried resin was separated into different wells. These wells of resin were independently reacted with amines, hydrozines, hydroxyamines, alcoholds, thioalcohols and other nucleophiles listed below for the building blocks. The resins were washed as above and treated with 2% TFA in dichloroethane to provide the corresponding libraries of nucleosides.

Scheme 13

4-Amino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **S3-2** (R_1 = H): To a solution of 8-bromo-4-amino-7-(2, 3, 5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **S3-1** (5.5 g, 8.06 mmol) in dioxane (50 ml) and NEt_3 (2.25 ml, 16.12 mmol) was shaken well under H_2 atmosphere (30 psi) in the presence of Pd/C (10%w/w, 500mg) for 16 h at room temperature. The reaction mixture was filtered over a Celite bed and washed with dioxane (2 x 50 ml). The filtrate was concentrated to give the crude product 4-amino-7-(2, 3, 5-tri–*O*–benzoyl-β-D-ribofuranosyl)-pyrrolo[2,3–d]–pyrimidine–5-carbonitrile in the quantitative yield (4.8g). This benzoate was then treated with saturated methanolic ammonia (100 ml) at room temperature for 16 h. The volatiles were evaporated, and the residue was purified over flash silica gel chromatography (fsgc) to give the title product **S3-2** (2.0g, 85% yield for two steps).

4-Oxo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **S3-3**. To a solution of S3-2 (2.0 g, 6.87 mmol) in water (40ml) and acetic acid (10 ml), $NaNO_2$ (4.74g, 68.7 mmol) was added and the reaction mixture heated at 70°C for 1 h. The volatile was evaporated and the residue was co-evaporated with pyridine (2 x 50ml). The residue was resuspended in pyridine (50ml) and then treated with acetic anhydride (5 ml, 53 mmol). After 16h at room temperature, MeOH (25 ml) was added and the volatile was evaporated. The residue thus obtained was dissolved in a mixture of water (100 ml) and

CH_2Cl_2 (300ml). The organic layer was separated, washed with water (200 ml) and brine (200 ml), dried (Na_2SO_4) and concentrated. The crude residue was then purified by flash chromatography on a silica gel column to provide the title product **S3-3** (2.1g, 73% yield for 2 steps).

4-Chloro-7-(-β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **S3-4.** A solution of **S3-3** (2.1 g, 5.02 mmoo) in $POCl_3$ (20 ml) was refluxed for 1 h. The cooled reaction mixture was poured into ice-water and stirred vigorously for 30min. The solid was filtered and washed with water. The hygroscopic solid was dried over P_2O_5 for 16 h under vacuum to give the crude 4-chloro-7-(2,3,5-tri-O-acetyl -β-D-ribofuranosyl)-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile **S3-4** (1.9 g). This compound was reacted in parallel with amine, hydroxyamines, hydrazines, and other nucleophiles as described in the building block lists. The reactions were treated with NaCN to provide the 7-deaza-7-substituted compounds **S3-5.** For the synthesis of 6-substituted 7-hydroxyamidine derivatives (**S3-5**, Z = C(=NH)NHOH), the above compounds were further treated with hydroxyamine at elevated temperature. For the synthesis of 6-substituted 7-amidine derivatives (**S3-5**, Z = C(=NH)NH2), the above compounds were further treated with ammonia at elevated temperature. The substituted amidine and hydroxyamidine derivatives were similarly synthesized by treating the cyano compounds with substituted hydroxyamines or substituted amines. Similar derivatives S3-5 with 2'-R1 were synthesized by the similar approach from the corresponding sugar modified 7-deaza-derivatives.

Triacetate compound **S3-4** was then treated with cold (-10°C) saturated methanolic ammonia and kept at 4°C for 2.5 h. The volatile was evaporated and the residue was purified by flash chromatography on a silica gel column to give the title product **S4-1** (1.1g, 77.56% yield for 2 steps). This compound was attached onto the solid support as described before.

Scheme 14

The reaction conditions described above for Scheme 13 were applied to Scheme 14 for the solid phase reactions to provide the libraries **S4-4** and **S4-5.**

Scheme 15

4-Amino-5-methoxycarbonimidoyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**S5-2**). Tri-*O*-benzoyl toyocamycin (12.60g, 30.19mmol) was suspended in 905 mL of methanol (30 mL/mmol) and stirred until completely dissolved. The reaction mixture was stirred at room temperature under the presence of argon. Then a 1N solution of MeONa/MeOH (11.0 mL, 11.0 mmol) was added to the reaction mixture and stirred at room temperature for 17 hrs. The reaction mixture was neutralized with a 1M solution of HCl (~10ml). The target compound was purified by silica gel chromatography (eluted with 500 ml of 8.0% MeOH/ EtoAc). Thus, the obtained compound (4.90g, 15.2 mmol) was suspended in a solution of MeOH (136.0 ml, 9 mL/mmol) and H_2O (379.0 mL/ mmol) stirred at 10^0 C, then a 1N solution of HCl (45.50mL, 45.4 mmol) was added. The reaction mixture was stirred at 10° C for ~6 hrs. 70 g of amberlite IRA-93 was added to the reaction mixture. The reaction mixture was filtered and the filtrate was concentrated which lead to a precipitate that was shown to be the target compound. Pyridine was added to the compound (4 mmol), followed by the addition of t-butylchlorodimethylsilane (1.1 eq.). The reaction mixture was stirred at room temperature for 24 h, then acetic anhydride (18 mL, 18 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. Pyridine was evaporated and the residue was extracted with ethyl acetate and water. The target compound **S5-2** was purified by silica gel chromatography (gradient of ethyl acetate in hexane).

N-Bromosuccinimide (5.5g, 31 mmol) was added to a solution of compound **S5-2** (7.0g, 16 mmol) in acetonitrile (240 mL). The reaction mixture was stirred at reflux temperature for 2 h. Acetonitrile was evaporated and the residue was purified by silica gel chromatography (gradient of ethyl acetate in hexane). Tributylphenyl tin (6.5 mL, 20 mmol) was added to a solution of the resultant compound (5.3 g, 10 mmol) and dichlorobis(triphenylphosphine)- palladium(II) ($Pd(PPh_3)_2Cl_2$) (0.7 g, 1.0 mmol) in degased *N,N*-dimethylformamide (150 mL). The reaction mixture was stirred at 85 °C for 48 h. The solvent was evaporated and the residue was purified by silica gel chromatography (gradient of ethyl acetate in hexane). Tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 11 mL) was added to a solution of compound e) (10 mmol) in tetrahydrofuran (100 mL). The reaction mixture was stirred at room temperature for 6 h. THF was evaporated and the residue was purified by silica gel chromatography (gradient of ethyl acetate in hexane) to provide compound **S5-3**.

A solution of compound **S5-3** (12 mmol) in 2,6-lutidine (1.9 mL) and anhydrous THF (36 mL) was added to a reaction vessel containing MMTCl-resin (4.5 g, 8.0 mmol). The reaction mixture was shaken at RT for 64 h. The reaction mixture was quenched by the addition of methanol (5 mL), followed by shaking for 30 min. The resin was then filtered, and washed with DMF (3×15 mL), MeOH (3×15 mL), and CH_2Cl_2 (3×15 mL). The washed resin was dried in vacuo at 45 °C overnight.

To a suspension of resin **S5-4** (5 mmol) in anhydrous THF (50 mL) was added triphenylphosphine (15 mmol), alcohols (15 mmol) and DEAD (15 mmol). The reaction mixture was shaken at RT for 24 h. The reaction mixture was filtered, and washed with THF (3×15 mL), MeOH (3×15 mL), and CH_2Cl_2 (3×15 mL). The washed resin was dried in vacuo at 45 °C overnight.

To a suspension of the resin **S5-5** obtained above (60 mg, 70 μmol) in toluene (0.5 mL) and NMP (0.5 mL), was added amino building blocks (1.4 mmol). The reaction mixture was shaken for 72 h at 95 °C. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight. A suspension of the resin above (70 mg, 0.07 mmol), in a methylamine solution (2.0 M in methanol, 1.2 mL), was shaken at 40 °C for 2 days. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight. To the resin obtained above (70 mg, 70 μmol) was added trifluoroacetic acid (1 mL, 1.5% in DCE). The reaction mixture was shaken for 5 min at rt. The solution was then filtered, and the filtrate evaporated to yield the desired libraries **S5-7** (R_1 and R_2 = H). The libraries with R_1 and R_2 of Me, Et, CH=CH2, and other groups were synthesized by the same approach under very similar conditions from the corresponding sugar modified nucleosides.

Scheme 16

The libraries **S6-6** were synthesized under conditions substantially identical to those described in scheme 15 above, however, without Heck/Stille/Suzuki reactions at the 8-position.

Scheme 17

7-Deaza-7-iodo-6-chloro-adenosine derivatives were shaken with MMT-Cl resin in 2,6-lutidine as described before. The resulted resins were reacted with amines and other nucleophiles (see building block lists) in the presence of DMP in pyridine and DMF. The Stille/Heck/Suzuki reactions at the 7-position provided resins **S7-4**, which were deprotected by ammonia and then cleaved from the solid phase with hexafluoroisopropanol to generate the libraries **S7-5**.

Scheme 18

Coupling of the (modified) sugar with the heterocyclic base to form the corresponding 7-deaza-8-aza nucleoside will follow a protocol substantially identical with the second reaction described in Scheme 11. Subsequent replacement of the chlorine in 6-position with various nucleophiles will follow reaction conditions substantially identical with those described in preceding Schemes (*e.g.*, Schemes 12 or 13) and it should be appreciated that such reactions may be readily performed by a person of ordinary skill in the art without expenditure of undue experimentation.

Scheme 19

Coupling of the (modified) sugar with the heterocyclic base to form the corresponding 7-deaza-8-aza nucleoside that is employed as starting material in Scheme 19 will follow a protocol substantially identical with the second reaction described in Scheme 11. It should further be recognized that reaction conditions for replacement of the p-nitrophenyl group with various nucleophiles (first derivatization) will generally follow procedures well known in the art. Similarly, derivatization of the amino group with various electrophilic reagents (second derivatization) may be readily performed by a person of ordinary skill in the art without expenditure of undue experimentation.

Scheme 20

Coupling of the (modified) sugar with the heterocyclic base to form the corresponding 9-deaza nucleoside will follow a protocol substantially similar to the second reaction described in Scheme 11. Subsequent replacement of the chlorine in 6-position with various nucleophiles will follow reaction conditions substantially identical with the fourth reaction

described in Scheme 11, and it should be appreciated that such reactions may be readily performed by a person of ordinary skill in the art without expenditure of undue experimentation.

Scheme 21

Again, coupling of the (modified) sugar with the heterocyclic base to form the corresponding 3-deaza nucleoside will follow a protocol substantially similar to the second reaction described in Scheme 11. Subsequent replacement of the leaving group (e.g., chlorine) in the 6-position with various nucleophiles will follow reaction conditions substantially identical with the fourth reaction described in Scheme 11, and it should be appreciated that such reactions may be readily performed by a person of ordinary skill in the art without expenditure of undue experimentation.

Exemplary Amino Building blocks (R-NH_2 or RNHR) used for the libraries

1-(Benzyl)benzylamine, 2-phenyl-n-propylamine, m-trifluorobenzylamine, 2,2-diphenylethylamine, cyclobutylamine, methylcyclohexylamine, 2-methylpropylamine, allylcyclopentanylamine, N-methyl-4-piperidinylmethylamine, 4-hydroxypiperidine, 3-hydroxypiperidine, 1-benzylpiperazine, p-methoxybenzylamine, N,N-bis(isopropyl)aminoethylamine, 2-ethylhexylamine, 5-methyl-2-furanosylmethylamine, N,N-dimethylaminopropylamine, 3-(N,N-dimethylamino)-2,2-dimethylpropylamine, 2-methylbutylamine, o-ethoxybenzylamine, 3-(2-methyl-N-piperidinylpropylamine, 1-(2-aminoethyl)pyrrolidine, 2-morpholinylethylamine, N4-hydroxyethylpiperazine, N-methylethylenediamine, 3-morpholinylpropylamine, pyridinyl-2-ethylamine, butylamine, hexylamine, methylamine, 2-hydroxyethylamine, N,N-dimethylethylenediamine, 3-methoxypropylamine, 2-methoxylethylamine, ethylamine, 2-isopropylamine, methylethylamine, 2-methylthioethylamine, di-n-butylamine, dimethylamine, allylamine, cyclopantylamine, 2-(N-methyl-pyrrolidin-2-yl)ethylamine, tetrahydrofuranosyl-2-methylamine, piperidine, N-benzyl-4-aminopiperidine, aminomethylcyclopropane, cyclopropylamine, 3-methylpiperizine, 4-piperidin-1-ylpiperidine, cyclohexylamine, piperazine, 4-pyridin-2-ylpiperazine, 1-methylpiperazine, N-(2-methoxyphenyl)piperazine, N-pyrimidin-2-ylpiperazine, cycloheptylamine, p-trifluorobenzylamine, benzylamine, 3-imidazol-1-ylpropylamine, exo-2-aminonorborane, N-phenylethylenediamine, 1-methylbenzylamine, 3,4-(1,3-dioxolanyl)benzylamine, pyridin-2-ylmethylamine, pyridin-3-

ylmethylamine, pyridin-4-ylmethylamine, thiophen-2-ylmethylamine, 3,3-dimethylbutylamine, o-methoxybenzylamine, 1-(3-aminopropyl)pyrrolidin-2-one, N-methylethylenediamine, m-methylbenzylamine, 3-methylbutylamine, 2-methylbutylamine, heptylamine, 3-butoxypropyamine, 3-isopropoxypropylamine, 2-morpholin-4-ylpropylamine, N1,N1-diethylethylenediamime, 2-ethylthioethylamine, 4-(2-aminoethyl)phenol, furfurylamine, 4-aminomethylpiperidine, 2-(2-aminoethyl)pyridine, 2-phenoxyethylamine, 2-aminoethylthiophene, p-methoxybenzylamine, 2-(N,N-dimethylamino)ethylamine, 1-amino-2-propanol, 5-methylfurfurylamine, 3-(dimethylamino)propylamine, o-methoxybenzylamine, 1-(3-aminopropyl)-2-pipecoline, hydrazine, 4-hydroxypiperidine, ethylenediamine, 1,4-diaminobutane, N-methylpropylamine, trans-1,4-diaminocyclohexane, 2,2,2-trifluoroethylamine, 3-chloropropylamine, 3-ethoxypropylamine, aminoacetaldehyde dimethyl acetal, 3-amino-1,2-propanediol, 1,3-diamino-2-hydroxypropane, 1-aminopyrrolidine, 2-(2-aminoethyl)-1-methylpyrrolidine, 3-methylpiperidine, 2-piperidine methanol, 3-piperidine methanol, 1-aminohomopiperidine, homopiperazine, 4-aminomorpholine, 3-bromobenzylamine, piperonylamine, 1,2,3,4-tetrahydroisoquinoline, L-proline methyl ester, 1-(2-pyridyl)piperazine, 4-(2-aminoethyl)morpholine, 1-(2-aminoethyl)piperidine, 3-aminopropipnitrile, 3-(aminomethyl)pyridine, 2-(aminomethyl)pyridine, thiomorpholine, 1,4-dioxa-8-azaspiro(4,5)-decane, 2-hydroxylethylamine, 1-(2-aminoethyl)pyrrolidine, aminomethylcyclohexane, 2-hydroxymethylpyrrolidine, 3-amino-1,2-propanediol acetone ketal, N-(2-hydroxyethyl)piperazine, N-phenylethylenediamine, 4-amino-2,2,6,6-tetramethylpiperidine, N-(4-nitrophenyl)ethylenediamine, 1,2-diphenylethylamine, 1-(N,N-dimethylamino)-2-propylamine, 2-phenylpropylamine, 2-methylcyclopropylamine, 2-methylaziridine, aminomethylcyclopropane, 1-aminomethyl-2-methylcyclopropane, butten-3-ylamine, 3-methyl-buten-2-ylamine, 3-methyl-buten-3-ylamine, 4-aminomethyl-1-cyclohexene, 3-phenylallylamine, 2,2-dimethylethylenediamine, 3-ethylhexylamine, 3-(N,N-dimethylamino)-2,2-dimethylpropylamine, 2-methyl-N-aminopropylpiperidine, as well as other related aliphatic and aromatic primary and secondary amine, hydrazine, hydroxyamine, various amino acid, amino acid ester derivatives that are good nucleophiles to react with leaving groups on the scaffolds.

Exemplary Building Blocks for C-C Bond Formation

For Heck Reaction: 2-ethynylpyridine, 5-phenyl-1-pentyne, 4-(tert-butyl)phenylacetylene, phenylacetylene, 3-dibutylamino-1-propyne, phenyl propargyl ether, 5-chloro-1-pentyne, 3-diethylamino-1-propyne, 4-phenyl-1-butyne, 1-heptyne, 1-dimethylamino-2-propyne, 1-pentyne, 2-methyl-1-hexene, (triethylsilyl)acetylene, 3-phenyl-1-propyne, methyl propargyl ether, 3-cyclopentyl-1-propyne, 1-ethynylcyclohexene, 3-butyn-1-ol, styrene, vinylcyclohexane, 2-(tributylstannyl)furan, 2-(tributylstannyl)thiophene, tetraphenyltin, 3-cyclohexyl-1-propyne, 4-methoxyphenylacetylene, 4-(trifluoromethyl)phenyleneacetylene, 4-fluorophenylacetylene, 4-pentayn-1-ol, 4-methylphenylacetylene, 1-ethynylcyclopentanol, 3-methyl-1-propyne, 5-cyano-1-pentyne, cyclohexylethyne, 1-ethynylcyclohexene, 5-cyano-1-pentyne, 1-dimethylamino-2-propyne, N-methyl-N-propargylbenzylamine, 2-methyl-1-buten-3-yne, cyclopentylethyne, 4-nitrophenylacetylene, phenyl propargylsulfide, 4-methyl-1-pentyne, propargyl ethylsulfide, 2-prop-2-ynyloxybenzothiazole, 4-ethoxy-1-prop-2-ynyl-1,5-dihydro-2H-pyrrol-2-one, 6-methyl-5-(2-propynyl)-2-thioxo-2,3-dihydro-4(1H)-pyrimidinone and related end-alkenes and alkynes.

For Stille Reaction: tetraethyltin, 2-(tributylstannyl)pyridine, tributylstannyl-4-t-butylbenzene, ethynyltri-n-butyltin, vinyltri-n-butyltin, allyltri-n-butyltin, phenylethynyltri-n-butyltin, phenyltri-n-butyltin, (2-methoxy-2-cyclohexen-1-yl)tributyltin, 5,6-dihydro-2-(tributylstannyl)-4H-pyran, tri-n-butyl(2-furanyl)tin, tri-n-butyl(2-thienyl)tin, tributyl(phenylethenyl)tin, 4-fluoro-(tri-n-butylstannyl)benzene, 5-fluoro-2-methoxy(tri-n-butylstannyl)benzene, 1-methyl-2-(tributylstannyl)-1H-pyrrole, 5-methyl-2-tributylstannylthiophene, 2-tributylstannylthiazole, 2-trybutylstannylpyrrazine, tributyl[3-(trifluoromethyl)phenyl]stannane and other related organic tin reagents.

For Suzuki Reaction: phenylboronic acid, 4-tolylboronic acid, 2-thiopheneboronic acid, thiophene-3-boronic acid, furan-2-boronic acid, cyclopentylboronic acid, 4-methylfuran-2-boronic acid, 3-hydroxyphenyl)boronic acid, 5-methylfuran-2-boronic acid, 3-cyanophenylboronic acid, 4-cyanophenylboronic acid, (5-formyl-3-furanyl)boronic acid, furan-3-boronic acid and other related organic boronic acids.

Exemplary Building Blocks ROH for Mitsunobu Reaction

1-Butanol, 4-nitrophenethyl alcohol, 4-chlorobenzyl alcohol, 1-propanol, 4-nitrobenzyl alcohol, 4-methylbenzyl alcohol, 2-butanol, benzyl alcohol, 2-methyl-1-propanol, crotyl alcohol, 2-norbornanemethanol, 2-methylcyclopropane-methanol, 3-buten-1-ol, neopentyl alcohol, cyclohexylmethanol, 4-trifluorobenzyl alcohol, 3-methyl-2-butem-1-ol, cyclopentanemethanol, 3-methyl-3-buten-1-ol, 4-methyl-1-pentanol, 3-chlorobenzyl alcohol, 3-cyclohexane-1-methanol, 3,3-dimethylbutanol, 3-trifluorobenzyl alcohol, cinnamyl alcohol, tetrahydrofurfuryl alcohol, ethanol, cyclopropyl alcohol, 1-methyl-3-piperidinemethanol, decahydro-2-naphthol, 9-decen-1-ol, 3-cyclopentyl-1-propanol, 1-methyl-2-pyrrolidineethanol, 3-methylbenzyl alcohol, 3-fluorobenzyl alcohol, 3-phenoxybenzyl alcohol, 4-isopropylbenzyl alcohol, 4-methoxybenzyl alcohol, 3,4-dimethoxybenzyl alcohol, 3,5-dimethylbenzyl alcohol, 4-benzyloxybenzyl alcohol, 2-phenylethanol, 4-fluorobenzyl alcohol, phenoxyethanol, benzyloxyethanol, 1-pentanol and 3-pentanol as well as aliphatic/aromatic/heterocyclic primary and secondary alcohols. Similar RSH derivatives have been used as building blocks for library synthesis.

All available aliphatic, aromatic and heterocyclic acyl chlorides, sulfonyl chlorides, isocyanates, thioisocyanates, carboxylic acids, amino acids, isocyanides, halogenated heterocycles for 2'- and 3'-NH_2 reactions.

BIOLOGICAL ASSAYS

The assays used to measure the inhibition of HCV NS5B and other polymerases, in vitro cell-based HCV replication, BVDV, HIV, RSV, HRV, HBV, influenza, and cytotoxicity are described below.

Assay of De Novo RNA Synthesis Activity for HCV NS5B Polymerase

All the oligoribonucleosides were purchased from Oligo etc. and were gel-purified. All the chemical reagents were of highest purity possible. H_2O used in the assay was RNase and DNase free. [α-^{33}P]-CTP (Ci/mmol) was purchased from ICN Biochemicals or Perkin-Elmer.

A typical assay reaction was carried out at 23°C for one hour in a buffer containing 20 mM Tris, pH 8.0, 20 mM MgCl2, 10 mM KCl, 5 % Glycerol, 5 mM DTT and 0.5 mg/ml

BSA. The template concentration was set at 10 mM and the enzyme concentration at 5 mM. The reaction was quenched by addition of a loading buffer (80% formamide, 100 mM EDTA, 50 mM Tris borate, 0.15% bromophenol blue and 0.15% of xylene cyanol) and heated to 70°C for 1 min prior to loading on a 1 X TBE polyacrylamide gel. Electrophoresis was performed in 1 X TBE at 3000 Volt. Gels were visualized and analyzed by using a PhosphorImager. Unless indicated otherwise, data are not shown for contemplated compounds.

HCV Replicon Assay

The replicon cells (Huh-7) contain replicating HCV replicon RNA, which was modified in the structural region (replacing the structural region with a neomycin resistance marker). Survival of the replicon cells under G418 selection relies on the replication of HCV RNA and subsequently expression of neomycin phosphoryltransferase. The ability of modified nucleoside libraries and compounds to suppress HCV RNA replication was determined using the Quantigene Assay Kit from Bayer. The assay measures the reduction of HCV RNA molecules in the treated cells. Replicon cells were incubated at 37°C for 3 days in the presence of nucleoside libraries and compounds before being harvested for detection. The HCV subgenomic replicon cell line was provided by Dr. Bartenschlager. The assay protocol was modified based on literature procedure (V. Lohmann, F. Korner, J. O. Koch, U. Herian, L. Theilmann, R. Bartenschlager, *Science*, **1999**, *285*, 110-113). Unless indicated otherwise, data are not shown for contemplated compounds.

Assay for Inhibition of BVDV

Bovine viral diarrhea virus (BVDV) (strain NADL) was provided by Dr. Ruben Donis and propagated in MDBK cells (ATCC). The nucleoside libraries and compounds were tested utilizing the modified protocol (V. B. Vassilev, M. S. Collett, R. O. Donis, *J. Viol.* **1997**, *71*, 471-478; S. G. Bagginski, D. C. Pevear, M. Seipel, S. C. C. Sun, C. A. Benetatos, S. K. Chunduru, C. M. Rice, M. S. Collett, *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 7981-7986). Unless indicated otherwise, data are not shown for contemplated compounds.

Hepatitis B Virus (HBV) Assay

The in vitro anti-HBV activity of nucleoside libraries and compounds was tested based on the reported protocol (W. E. Delaney, 4th, R. Edwards, D. Colledge, T. Shaw, J. Torresi, T. G. Miller, H. C. Isom, C. T. Bock, M. P. Manns, C. Trautwein, S. Locarnini, *Antimicrob. Agents Chemother.*, **2001**, *45*, 1705-1713; W. E. Delaney, 4th, T. G. Miller, H. C. Isom, *Antimicrob. Agents Chemother.*, **1999**, *43*, 2017-2026; B. E. Korba, J. L. Gerin, *Antiviral Res.*, **1992**, *19*, 55-70). Unless indicated otherwise, data are not shown for contemplated compounds.

Human Immunodeficiency Virus (HIV) Assay

The in vitro HIV-1 activity of nucleoside libraries and compounds was tested utilizing the following modified protocol. Freshly isolated human PBMCs from healthy donors were infected with HIV-1 isolates for 3 hours. The cells were then washed three times to remove the viruses. The infected cells were plated into 96-well tissue culture plates and incubated for 7 days in the presence of serially diluted nucleoside analogues (with a medium change at day 4). A standardized HIV-1 p24 Elisa was performed to measure the extent of HIV replication in the presence of the compounds. (C. J. Petropoulos, N. T. Parkin, K. L. Limoli, Y. S. Lie, T. Wrin, W. Huang, H. Tian, D. Smith, G. A. Winslow, D. J. Capon, J. M. Whitcomb, *Antimicrob. Agents Chemother.*, **2000**, *44*, 920-928; Parkin, N. T., Y. S. Lie, N. Hellmann, M. Markowitz., S. Bonhoeffer, D. D. Ho, C. J. Petropoulos, *J. Infect. Disease*, **1999**, *180*, 865-870). Unless indicated otherwise, data are not shown for contemplated compounds.

Human Rhinovirus (HRV) Assay

The in vitro activity of nucleoside libraries and compounds against HRV was tested based on the reported protocol (W.-M. Lee, W. Wang, R. Rueckert, *Virus Genes*, **1994**, *9*, 177-181; B. Sherry, R. Rueckert, *J. Virol.* **1985**, *53*, 137-143). Unless indicated otherwise, data are not shown for contemplated compounds.

Respiratory Syncytial Virus (RSV) Assay

The RSV activity of nucleoside libraries and compounds was tested based on the reported protocol. Respiratory syncytial virus (strain A-2) was purchased from ATCC and virus stock was obtained by propagating the virus in Hep-2 cells. (P. R. Wyde, L. R.

Meyerson, B. E. Gilbert, *Drug Dev. Res.* **1993**, *28*, 467-472). Unless indicated otherwise, data are not shown for contemplated compounds.

Yellow Fever Virus (YFV) Assay

Yellow fever virus (vaccine strain 17-D) was purchased from ATCC (VR-1268) and the virus stock was obtained by infecting SW-13 cells from ATCC. The YFV activity of nucleoside libraries and compounds was tested utilizing the reported protocol (J. J. Schlesinger, S. Chapman, A. Nestorowicz, C. M. Rice, T. E. Ginocchio, T. J. Chambers, *J. Gen. Virol.* **1996**, *77*, 1277-1285). Unless indicated otherwise, data are not shown for contemplated compounds.

Influenza Virus Assay

Influenza virus (type A, A/PR/8/34) was produced by infecting pathogen-free fertilized chicken eggs. The antiviral assay was performed on Madin Darby canine kidney (MDCK) cells from ATCC based on the reported protocol (E. H. Nasser, A. K. Judd, A. Sanchez, D. Anastasion, D. J. Bucher, *J. Virol.* **1996**, *70*, 8639-8644). Unless indicated otherwise, data are not shown for contemplated compounds.

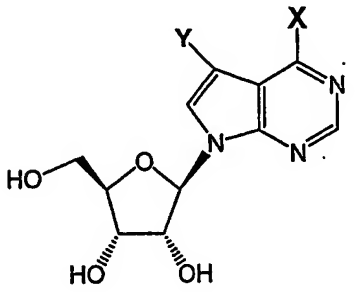
Cytotoxicity Assay

The cytotoxicity of nucleoside libraries and compounds was measured by the MTS cell based assay from Promega (CellTiter 96 Aqueous One Solution Cell Proliferation Assay). Unless indicated otherwise, data are not shown for contemplated compounds.

Exemplary Data for Selected Contemplated Compounds

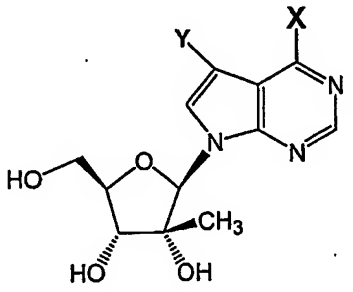
The following results are data obtained using the HCV replicon assay as described below, and the letters A, B, and C indicate EC_{50} values of less than 10 μM, between 10 and 100 μM, and over 100 μM, respectively.

Table 1. Anti-HCV Results of Exemplary 7-deaza Compounds



Compound	7-substitution Y	6-substitution X	HCV Replicon EC_{50}
6	C(=NH)NHOH	$N(CH_3)_2$	A
7	$C(=NH)NH_2$	$N(CH_3)_2$	A
8	C(=NH)NHOH	SCH_3	A
10	N(=NH)NHOH (5'-Ac)	$NHCH_3$	A
11	C(=NH)NHOH	$NHCH_3$	B
13	CN	$N(NH_2)CH_3$	A
14	$C(=NOH)NH_2$	NHOH	A
19	$N(=NHNH_2)NHNH_2$	H	A

Table 2. Anti-HCV Results of Exemplary 2'-beta-methyl-7-deaza Compounds



Compound	7-substitution Y	6-substitution X	HCV Replicon EC_{50}
24	C(=NH)NHOH	$NHCH_3$	B
26	N(=NH)NHOH	$N(CH_3)_2$	C
28	C(=NH)NHOH	OH	C
30	C(=NH)NHOH	NH_2	A
32	$CONH_2$	NHOH	C
34	$C(=NH)NH_2$	NHOH	A
35	CONHOH	NHOH	C
36	C(=NH)NHOH	NHOH	B
38	C(=NH)NHOH	SCH3	B
40	$CONH_2$	$NHNH_2$	C

Consequently, it is contemplated that the compounds according to the inventive subject matter may be employed in pharmaceutical compositions to treat various viral diseases. In an especially preferred aspect of the inventive subject matter, the inventors contemplate a method of inhibiting replication of a virus in which one or more of the compounds according to the inventive subject matter are provided. In a further step, the virus is presented with the compound(s) at a concentration effective to inhibit replication of the virus. The term "presenting the virus with a compound" as used herein broadly refers to all manners in which the virus or viral component is incubated with the compound.

For example, where the virus or viral component (particularly including a viral RNA dependent RNA polymerase) is in an *in vitro* system, presentation may comprise admixing the medium in which the virus or viral component is disposed with the compound. In another example, where the virus or viral component is in a cell (either in a cell culture, or *in vivo* in a hepatocyte in an infected liver of a mammal) it is contemplated that the step of presenting may include administration of a pharmaceutical composition comprising contemplated compounds to the organism in which the virus or viral component is disposed. Suitable pharmaceutical compositions may include oral, parenteral, transdermal, and various other

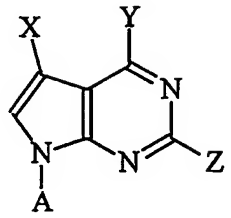
known pharmaceutical compositions. Hence, in an especially preferred aspect, the virus is an HCV virus and is disposed within a cell (which is preferably a hepatocyte in a liver infected with the virus).

Thus, specific embodiments and applications of deazapurine nucleoside compounds and uses as antiviral agents have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

CLAIMS

What is claimed is:

1. A compound according to Formula 1



Formula 1

wherein A is a sugar in D- or L-configuration;

X is H, alkyl, CN, C(R')NR"R'", NR"R'", NR"NR"R'", NHO-alkyl, N_3, S-alkyl, S-alkenyl, S-alkynyl, O-alkyl, O-alkenyl, O-alkynyl, or ONH_2;

Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'" ;

Z is H or NH_2;

wherein R' is O, NH, NNH_2, NOH, or S, and wherein R" and R'" are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl; and

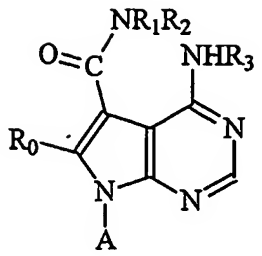
with the proviso that when A is D-ribofuranosyl and X is H, then Y is not OH or H, and Z is not H or NH_2.

2. The compound of claim 1 wherein A is 2'-beta-methyl-D-ribofuranosyl, and X is alkyl, CN, C(R')NR"R'", NR"R'", NR"NR"R'", NHO-alkyl, N_3, S-alkyl, S-alkenyl, S-alkynyl, O-alkyl, O-alkenyl, O-alkynyl, or ONH_2.

3. The compound of claim 2 wherein Y is C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'".

4. The compound of claim 3 wherein Z is H.

5. A compound according to Formula 2



Formula 2

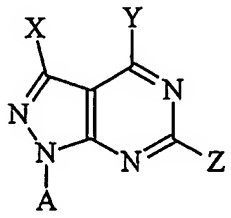
wherein A is a sugar in D- or L-configuration; and

wherein R_0, R_1, R_2, and R_3 are independently H, OH, halogen, or optionally substituted alkyl, alkenyl, alkynyl, or aryl.

6. The compound of claim 5 wherein A is 2',3'-beta-dimethyl-D-ribofuranosyl.

7. The compound of claim 6 wherein R_0 is H and wherein R_1, R_2, and R_3 are independently optionally substituted alkyl, alkenyl, alkynyl, or aryl.

8. A compound according to Formula 3



Formula 3

wherein A is a sugar in D- or L-configuration;

X is H, optionally substituted alkyl, CN, C(R')NR"R'", C(O)OR", or NR"R'";

Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'";

Z is H, NH_2, NHC(O)R", NHNHC(O)R", NHNHC(S)R", or $NHS(O)_2R$"; and

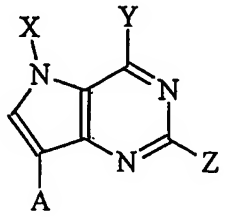
wherein R' is O, NH, NOH, or S, and wherein R" and R'" are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl.

9. The compound of claim 8 wherein A is 2'-beta-methyl-D-ribofuranosyl.

10. The compound of claim 9 wherein X is C(R')NR"R'", C(O)OR", or NR"R'".

11. The compound of claim 10 wherein Y is C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'".

12. A compound according to Formula 4



Formula 4

wherein A is a sugar in D- or L-configuration;

X is H, optionally substituted alkyl, CN, C(R')NR"R'", C(O)OR", or NR"R'";

Y is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'";

Z is H, NH_2, NHC(O)R", NHNHC(O)R", NHNHC(S)R", or $NHS(O)_2R$"; and

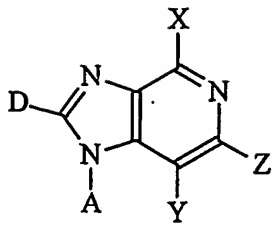
wherein R' is O, NH, NOH, or S, and wherein R" and R'" are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl.

13. The compound of claim 12 wherein A is 2'-beta-methyl-D-ribofuranosyl.

14. The compound of claim 13 wherein X is C(R')NR"R'", C(O)OR", or NR"R'".

15. The compound of claim 14 wherein Y is C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'".

16. A compound according to Formula 5



Formula 5

wherein A is a sugar in D- or L-configuration;

D is H, halogen, alkyl, alkenyl, alkynyl, or aryl;

X is H, CN, alkyl, C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'";

Y is H, alkyl, alkenyl, alkynyl, or aryl;

Z is H or NH_2; and

wherein R' is O, NH, NOH, or S, and wherein R" and R'" are independently H, OH, O, NH_2, NH, O-alkyl, alkyl, alkenyl, alkynyl, or aryl.

17. The compound of claim 16 wherein A is 2'-beta-methyl-D-ribofuranosyl.

18. The compound of claim 17 wherein D is H.

19. The compound of claim 17 wherein X is C(O)OR", C(R')NR"R'", OH, S-alkyl, or NR"R'".

20. The compound of claim 19 wherein Y is H.

21. A method of inhibiting replication of a virus, comprising:

providing a compound according to any one of claims 1, 5, 8, 12, or 16;

presenting the virus with the compound at a concentration effective to inhibit replication of the virus.

22. The method of claim 21 wherein the virus is an HCV virus.

23. The method of claim 22 wherein the virus is disposed in a cell.

24. The method of claim 23 wherein the cell is a hepatocyte in a liver infected with the virus.